A Dissertation on

Evaluation of Sentinel Lymph Node Assisted Neck Dissection Using Methylene Blue Dye in Oral Cavity Cancers

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BONAFIDE CERTIFICATE

This is to certify that **Dr. P. Kathirvel kumaran,** bonafide student of M.Ch. Surgical Oncology (August 2010 to August 2013) in the Department of Surgical Oncology, Government Royapettah Hospital, Chennai – 600 014 has done this dissertation on "**Evaluation of Sentinel Lymph Node Assisted Neck Dissection Using Methylene Blue Dye in Oral Cavity Cancers"** under my guidance and supervision in partial fulfillment of the regulations laid down by The Tamilnadu Dr. M.G.R. Medical University, Chennai for M.Ch. Surgical Oncology Examination to be held in August 2013.

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INTRODUCTION

Carcinoma of the oral cavity is the second most common cancer in India and fourth most common in Madras Metropolitan Tumor Registry [(1)]. Cervical nodes form the first echelon of metastases in cancers of the oral cavity. The frequency of cervical nodal metastases varies depending on the subsite, tumour size, depth of invasion, tumour grade, etc. The treatment of cervical nodal metastases from oral cancers depends on the number, size, and level of nodal spread; it can be surgery, radiation, chemotherapy or their combinations. Clinically node negative (N0) patients form a specific subset among oral cancers for whom the treatment of neck is not well standardised. Treatment options include observation, elective neck dissection or elective neck irradiation and depends on various factors like risk category, patient preference, treatment availability, treatment for the primary, physician preference etc. The chance of occult metastases in clinically N0 disease can be up to 30 percent [(2)]. Elective treatment of neck is recommended in high risk groups defined as those patients with risk of lymph node metastasis risk more than 20 percent [(3).] If the neck is not addressed while adequately treating the primary, there is a high chance of nodal recurrence in those patients who harbor metastases [(3).]

Clinical examination with imaging modalities like ultrasound, computed tomography (CT) scan, magnetic resonance imaging (MRI) and positron emission tomography (PET) scan are not sensitive enough to exclude occult neck nodes in clinically N0 patients[(3)].

Sentinel lymph node is the first echelon node and often first site of metastases. Histological status of sentinel node may predict micro-metastases in the reminder of

lymphatic basin. The technique of Sentinel lymph-node biopsy (SLNB) has been successfully applied in carcinoma of breast and melanoma. Extrapolating these concepts, it would be ideal to do a complete neck dissection only in patients with positive sentinel nodes. This could spare the morbidity of the neck dissection in up to 70 percent of patients [(4)]. With this background we tried to evaluate sentinel lymph node using methylene blue dye in clinically node negative oral cavity cancers at Government Royapettah Hospital.

AIM OF THE STUDY

Primary Aim:

The primary aim of this study is to evaluate the feasibility and efficacy of sentinel lymph node using methylene blue dye in clinically node negative early stage oral cavity cancers in avoiding morbidity of neck dissection.

Secondary Aims:

(1) To identify most common site of sentinel lymph node for oral cancers.

(2) Usefulness of USG imaging in assessing neck metastasis not apparent clinically.

(3) Correlation of sentinel node with non-sentinel node metastases

(4) Assessing possibility of level IIB, IV and V sparing neck dissections in oral cancers N0 neck

REVIEW OF LITERATURE

Introduction:

Carcinoma of oral cavity is more prevalent in the areas of tobacco abuse. It is more common in men, with a male to female ratio of 2.3:1[(5)]. The risk of nodal metastases increases with increasing "T' status and grade of the tumor and specific subsites like tongue, FOM and alveolus. The presence of metastatic neck node is the single most important adverse prognostic factor. The 5-year survival rate decreases to below 50 percent when cervical nodal metastases are present [(6,7,8)]. The lymphatic metastases from head and neck cancers follow a well-defined pattern. In the absence of metastasis to levels I, II and III, the involvement of levels, IV and V are rare (exception being tongue) [(7).]

Lymphatic Anatomy:

The prime function of the lymphatic system is the return of proteins, interstitial fluid and immune cells back to the bloodstream. These elements initially enter the lymphatic capillary vessels which are lined by non-gapped continuous endothelial cells. Lymphatic fluid flows in smaller collecting vessels (2 layered) and then into larger collecting vessels (3 layered), which finally drain into lymph nodes [(9)] [(fig-1)]. Afferent lymphatic vessels enter the convex surface of lymph node and drain into the marginal sinus. Medullary sinuses receive lymph from the marginal sinus and penetrate the medulla of the lymph node. Efferent lymphatic vessels formed by coalescence of lymphatic channels in medulla exit via the hilum. Lymph flows through the node in a unidirectional manner. Afferent lymphatics may at times bypass certain lymph nodes in their path [(10).]

Variations in anatomy of lymphatics have been described by Ludwig [11] (Figure 2).

Figure 1 Lymph Node Anatomy

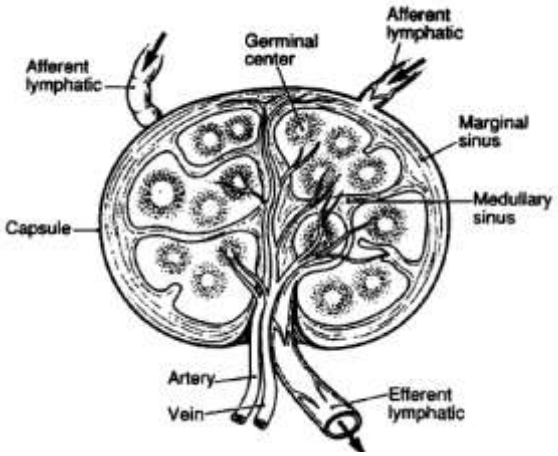
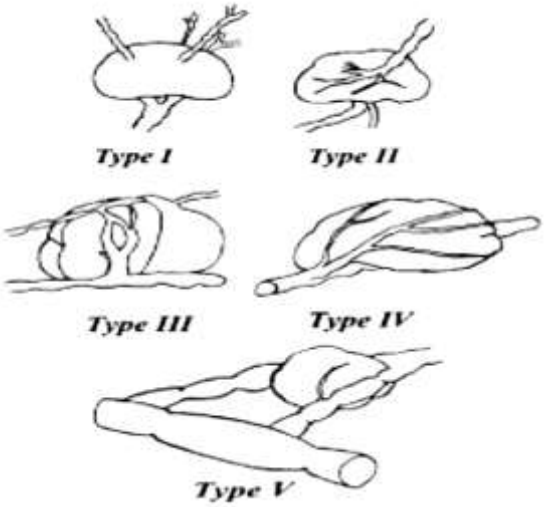


Figure 2 Types of Lymphatic Drainage



Lymphatic Flow Pattern in Head and Neck:

The head and neck region has a dense and complicated network of lymphatic channels. It accounts for a third of the total number of lymph nodes in the human body (approximately 200 to 350 lymph nodes). Lymph nodes of the head and neck are divided into superficial and deep groups. The superficial lymphatics and nodes lie between the skin and the superficial fascia. Deep cervical nodes are present deep to the sternocleidomastoid muscle, along the internal jugular vein from the base of skull to the brachiocephalic junction. Efferent lymphatics drain into the venous system at that junction.

Lymphatic drainage from specific regions of the Upper-Aero-Digestive-Tract (UADT) [12,13] follow a predictable pattern according to the preferential pathways of natural lymph flow (Werner and Davis[14]). Lymphatics of the neck have been organized into four functional drainage pathways 1). The main lymphatic pathway, 2).The posterior pathway, 3). The anterior lymphatic pathway and 4). The superficial-lateral pathway. The works of Lindberg, Byers et al. [15] (1988), and Shah et al. [16] (1990) were among the many studies that were vital in understanding the lymphatic basins at risk of metastasis from Squamous Cell Carcinoma (SCC) arising from specific sub-sites of the UADT.

However, it is important to emphasize that, inspite of these widely accepted generalized patterns of lymphatic drainage; there is wide variability in the lymphatic flow of the head and neck region [17]. This variability is confirmed by studies performed at the Moffit Cancer Center, Miami, which has shown as much as a 63 percent discordance between a patient's predicted lymphatic drainage based on classic

pathways as opposed to the patient's actual lymphatic anatomy imaged by a lymphoscintigram[17]

In 2004, American Head and Neck Society agreed upon a classification system of six lymph node levels proposed by Robbins et al., 2000[18] which has been widely accepted. Knowledge of the primary tumor site and understanding of the pathways of lymphatic tumor spread helps to predict the region of the neck at highest risk for metastatic disease.

Lymphatic drainage of oral cavity [19]:

Lymph from the central part of the lower lip drains to the submental lymph nodes. Lateral parts of the lower lip, upper lip and the mucous membrane of the cheek drain to the submandibular lymph nodes. Both surfaces of the lower gingivae and the outer surface of the upper gingivae drain into submandibular lymph nodes. The inner surface of the upper gingiva is drained by the vessels of the hard palate to the upper deep cervical lymph nodes. The floor of the mouth drains anteriorly via lymphatics that pierce the mylohyoid muscle to reach the submental nodes or posteriorly to the submandibular nodes. The submandibular and submental nodes drain into the deep cervical nodes from where the lymph finally empty in the jugular trunk.

Types of Neck Dissections [20]:

Treatment options of the neck in clinically node positive patients (N+) mostly depend on the treatment of the primary lesion. Radiation or chemo radiation to the neck is given if primary lesion is treated by radiation, and neck dissection should be performed if primary lesion is managed by surgery. An academic classification of neck dissections is shown in Table 1 and the types are described below.

Table 1 Classification of Neck Dissections

Neck dissections classification	
Comprehensive Neck Dissections	**Selective Neck Dissections**
Radical neck dissection. Modified radical neck dissection Extended radical neck dissection	Supraomohyoid neck dissection (level I-III). Posterolateral neck dissection (level II, III, IV, V) Lateral neck dissection (Level II-IV) Anterior neck dissection (VI)

1. Radical neck Dissection:

In radical neck dissection, all cervical lymph node groups from levels I to V were removed as enbloc with the Spinal Accessary Nerve, Internal jugular vein, and Sternocliedomastoid muscle on one side.

2. ***Modified Radical Necks Dissection:***

In modified radical neck dissection, all lymph nodes routinely removed by the radical neck dissection are removed with preservation of one or more the important non lymphatic structures i.e. Spinal Accessary Nerve, Internal jugular vein, and Sternocliedomastoid muscle.

3. Extended Neck Dissection:

Extended neck dissection refers to the removal of one of more additional lymph node groups' like retropharyngeal, superior mediastinal, buccinators and para tracheal lymph nodes and/or non lymphatic structures like the hypoglossal nerve, vagus nerve, paraspinal muscles, skin, external carotiod, etc.

4. Selective Neck Dissection:

A selective neck dissection refers to dissection of lymph node groups which are at high risk of involvement based on the lymphatic anatomy of the primary. For oral cavity cancers, the lymph nodes at greatest risk are located in levels I, II, and III. The lymph nodes at risk for oropharyngeal, hypopharyngeal, and laryngeal cancers are located in levels II, III, and IV, for thyroid cancer the lymph nodes are level VI, II, III, IV, V. (Table 1)

If a neck dissection is carried out when there is no evidence of neck disease it is termed an "elective" neck dissection (END). Some authors use the word "prophylactic" instead of "elective" to denote the same procedure. If the neck dissection is undertaken for metastatic disease in the neck it is called a "therapeutic" neck dissection

Clinically Node Negative Patients (N0):

Though the treatment of neck in N+ patients has been well studied and established, the treatment of neck in clinically N0 patients remains controversial. Clinically N0 patients harbor a risk of having occult metastases in the neck in upto 30 percent. Patients with high risk for occult metastasis,[6,7,8] are identified by characteristics of the primary lesion thickness of >4 mm and size >2 cm, anatomic location, lympho vascular invasion, perineural infiltration, poorly differentiated histology and immunosuppression.(Table 2) Cervical node metastasis is the single most important adverse prognostic factor with drop in overall 5 years survival from 82 to 53 percent. Hence it seems logical to intervene early rather than watchful waiting, as delayed resection in clinically evident macroscopic disease have poor prognosis [21].

Table 2 Risk of Occult Neck Node Metastases in Oral Cancers

Group	Risk of occult metastases	Stage	Primary site
High risk	>30%	T1-4	Nasopharynx, pyriform sinus, base of tongue
		T2-4	Soft palate, pharyngeal wall, supraglottic larynx, tonsil
		T3-4	Anterior 2/3rd tongue , FOM, RMT, Gingiva, Hard palate, Buccal mucosa
Intermediate risk	20-30%	T1	Anterior 2/3rd tongue, soft palate, pharyngeal wall, supraglottic larynx, tonsils
		T2	Anterior 2/3rd tongue , FOM, RMT, Gingiva, Hard palate, Buccal mucosa
Low risk	<20%	T1	FOM, RMT, Gingiva, Hard palate, Buccal mucosa

Modalities for treatment of N0 neck: [22,23]

The management options for the clinically N0 neck include (1) selective neck dissection with the rationale of regional staging and elective treatment, (2) irradiation of the neck as elective treatment, and (3) observation- clinical follow-up with option of therapeutic neck dissection or irradiation if patients develop detectable neck nodal disease.

Elective irradiation of neck has several limitations. It is more morbid and provides no staging information to estimate prognosis or guide further management. Few treatment alternatives exist in those who develop second primary tumors which occurs in about 2-4%/year [(23)].

Selective neck dissection (I-III) offers comparable local control rates with less morbidity when compared with radiotherapy and other types of neck dissection in SCC of oral cavity. Sometimes close observation is sufficient if the primary lesion is of T1 stage.

More precise staging before treatment is mandatory to prevent the consequences of inappropriately selected management strategies for the clinically N0 neck in oral cancer. The concept of sentinel node biopsy may fulfill the requirement. The surgeon should have experience with a minimum of 10 cases before undertaking SLNB as a staging tool.

Methods to identify occult lymph node metastases:

1. **Noninvasive methods:**

The radiological assessment of neck in clinically node negative patients has improved with recent advances in imaging techniques. Contrast-enhanced CT and MRI are the common imaging modalities used to evaluate the neck in oral cancers. Radiological criteria for nodal involvement include size (Levels I, II ≥ 1.5 cm, Levels III – VI ≥ 1.2 cm), number of nodes (3 lymph nodes > 8 mm), central necrosis, irregular enhancement and poorly defined or irregular capsules [(24,25)]. PET scan has poor sensitivity in detecting micro-metastases in the neck [(26)]. The combined use of ultrasound with fine needle aspiration may also identify patients requiring neck

dissection [27]. However the available methods reach only 80–85% sensitivity and require experienced and skilled operators [27]. (Table 3)

Table 3: Comparison of imaging modalities in Occult Metastases in N0 Neck

Modality	Sensitivity	Specificity
Ultrasound [24]	50-58%	75-82%
CT[24]	40-68%	78-92%
MRI[24]	55-93%	82-95%
PET[26]	87-90%	80-93%
CT-PET[26]	96%	98.5%

2. **Invasive methods:**

1. Pre-operative dynamic / static scintigraphy with or without SPECT
2. Blue dye technique
3. Hand held Gamma probe aided detection of SLNB.
4. Combination of two or more techniques.

Sentinel lymph node biopsy - Historical perspective

Regional lymph node dissection (RLND) is based on existing knowledge of tumour spread through lymphatics. The varied frequency of lymph node metastases in various cancers depending on the primary tumour characteristics challenges the role for routine RLND or its modifications in all patients with nodal disease. Sentinel node biopsy may offer a solution to this dilemma.

In 1955, Seaman and Powers [28] laid the groundwork for lymphoscintigraphy and lymphatic mapping. Gould et al [29] independently observed that the routine

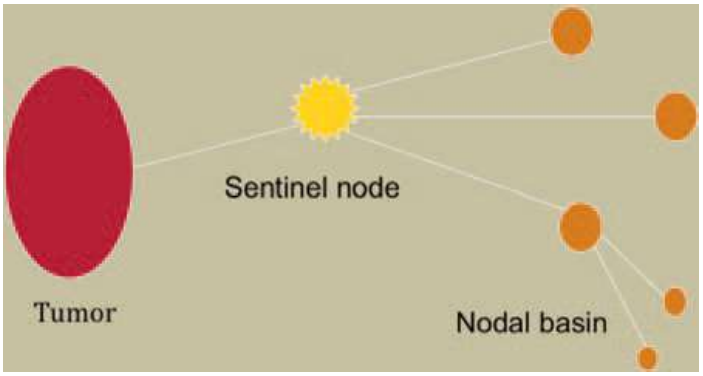
excision of a ‘‘sentinel node’’ found at the origin of the common facial vein at the time of parotidectomy offered diagnostic significance. The ‘‘Cabanas approach [30], introduced in 1977 is less reliable because of the relatively crude localization techniques based on anatomy only. In 1992 Morton [31] et al used cutaneous lymphoscintigraphy as a method to identify the nodal basins at risk of metastases in melanomas located in ambiguous sites. Alex and Krag [32] in 1996 reported the first successful sentinel node biopsy in a case of supraglottic cancer. While lymphoscintigraphy improved and assay techniques increased in sensitivity, preferential drainage to one or two nodes in the lymph nodal basin was consistently demonstrated which made application of SNB technique more common [33].

Sentinel Lymph Node Biopsy – Concept and Principles

Tumour cell progression within the lymphatic system follows an orderly pattern. Primary or the draining lymph nodes possess the structural and functional capability to filter and entrap tumour cells efficiently. Thus removing uninvolved lymph nodes may be harmful to the patient from an immunological point of view.

Sentinel node biopsy is a minimally invasive, diagnostic procedure which can accurately predict the presence/ absence of nodal metastases. It offers a reliable method to avoid lymphadenectomy. The success of SLNB depends on two factors: the accuracy of the localisation technique to identify the sentinel lymph node, and its intraoperative feasibility. The finding of gross cancer involvement contraindicates sentinel node biopsy and mandates formal lymphadenectomy.

Figure 3: Concept of Sentinel Lymph node



The three essential principles of SLNB are: [34]

1. A predictable and orderly pattern of tumour spread from the primary to regional lymph nodes.
2. The lymph node effectively filters the afferent lymph whereby the tumour cells get entrapped in it.
3. There is a sequential progression of tumour cells from the first echelon to second echelon nodes.
4. Unidirectional spread due to lymphatic valves.

There is sufficient evidence available to support these three basic principles in head and neck cancers [35,36].

Sentinel Lymph Node Biopsy (SLNB) is applicable for staging the following [37]:

1. Ipsilateral clinically N0 neck drained by a unilateral primary tumor
2. Bilateral clinically N0 neck drained by a midline tumor or crossing the midline

3. Contralateral clinically N0 neck drained by a midline tumor or tumor crossing the midline in the presence of a clinically positive ipsilateral neck.

De Boer et al[38] showed a statistically significant difference in disease free survival (DFS) in head and neck cancers between SLN-negative and patients with micro metastases or ITCs. Pitman KT [39] et al showed that patients with micro metastases had an intermediate prognosis between patients who are node-negative and those with macro metastases. Sentinel lymph nodes identified in the context of elective neck dissection is called as SNB-assisted elective neck dissection [39].

Additional pathologic methods of serial sectioning and immunohistochemical analysis of sentinel nodes have upstaged up to 8% of neck dissection specimens in patients with head and neck [40].

To date, SLNB can be considered as the most accurate way to stage the cN0 neck[41] .The SLN with the highest radioactive count may be the most likely to harbor tumor cells. Studies in patients with breast cancer reported a considerable false-negative rate of SLNB (9% to 29%) if only the hottest SLN was removed.[42] Atula et al[43] demonstrated that, in Oropharyngeal SCC it was sufficient to dissect the 3 hottest lymph nodes to detect occult metastases in all patients.

Sentinel Lymph Node Biopsy - Physiology of Lymphoscintigraphy: [44-46]

Lymphoscintigraphy (LS) is the study used for localization of lymph nodes draining a specific anatomic area. It uses after intraepithelial, subepithelial, or intra-parenchymal injection of identifiable particles of appropriate size into the interstitium. The particles enter lymphatic capillaries and flow to the lymph nodes where they are phagocytosed by macrophages. Successful SLNB requires patent lymphatic channels as well as normally functioning lymph nodes. It also requires that the percentage of

particles trapped in the more proximal nodes is greater than the percentage of particles that flow to distal lymph nodes. 99mTc sulfur colloids are common for lymphoscintigraphy. The advantages are:

1. They emit only gamma rays and have low radiation exposure
2. Half-life is only 6 hr and peak energy emission peak of 140 keV, within the detection range of most handheld gamma probes.

Particle size is the primary factor that determines the rate of uptake and filtration within the sentinel node. The optimal particle size of radioisotopes is between 5 and 10nm. Particles smaller than 5nm are absorbed by the vascular system.

SLNB usually uses a triple diagnostic approach. Twenty four hours prior to operation, radiocolloid is injected around the primary tumor site and static lymphoscintigraphy is used to identify the location of the sentinel node(s). Intraoperative identification is done using both blue dye and hand-held gamma probe.

Sentinel Lymph Node Biopsy - Lymphoscintigraphy Technique:

Static and dynamic imaging, are two modes of obtaining lymphoscintigraphy. Optimum pre-operative information is obtained by dynamic imaging, due to the short distance from primary site to sentinel node, complexity of the anatomy and variable pattern of lymphatic drainage.

Early imaging (<30 min post injection)

i) SLNB- Hotspots with evident uptake

ii) 2^{nd} echelon - Caudal hotspot with clearly visible connecting lymphatic vessel from a cranial hotspot, not increasing in time

iii) Caudal hotspot with low uptake not increasing in time

Late static imaging (2–4 hr post injection)

i) SLNB-New hotspots visualized ipsilaterally or contralaterally.

ii) New hotspots visualized between a hotspot already identified during early imaging and the injection site.

iii) Caudal hotspots with a previously low uptake, but now much more intense.

iv) Newly visualized hotspot also considered to be a sentinel node.

Tumors in the oral cavity other than mobile tongue and FOM tumors seem to have slower lymphatic drainage; an early lymphatic imaging was able to identify hotspots in only 29% of patients with these tumors [(44)]. Heuveling et al [(44)] believes that late lymphoscintigraphic imaging should be considered for these tumors to minimize the risk of false-negative results. The same is true for paramedian and midline tumors, for which bilateral drainage was observed in the majority (83%) of tumors, half of them visible only during late imaging [(44)].

SLNB may also prove useful for those patients with clinically established ipsilateral neck disease, with an N0 contra-lateral neck clinically but are at risk of contra-lateral neck involvement [(44)]. In such patients lymphoscintigraphy may establish the presence of bilateral drainage, and sentinel node biopsy can spare them the morbidity of elective treatment to opposite neck. SPECT/CT offers better anatomical localisation than planar lymphoscintigraphy but may not improve the outcome of the sentinel node procedure itself [(46)]. Acquisition time of SPECT is much longer compared with that of planar lymphoscintigraphy, and SPECT imaging is often performed as the final imaging procedure – that is, at a later time point after injection of 99mTc-Nanocoll – second echelon lymph nodes containing radiocolloid

may become visible on SPECT images [46]. Furthermore, additional hotspots detected next to the hotspot that was identified on planar LS should also be detected intraoperative by the gamma probe. Haerle et al [46] believe that SPECT-CT imaging is a helpful additional tool for detailed localization of a hotspot, but not for identification of true SNs.

Sentinel Lymph Node Biopsy – Using the Gamma camera [47]:

A hand held Gamma camera probe is used for detection of radioactivity. It should be passed slowly over the neck at a steady rate, aimed away from the primary resection bed to assess the auditory input for radioactivity. As the probe measures radioactivity with time, rapid or unsteady movement leads to higher readings and louder auditory input, and should be avoided. Any lymph node with atleast 10% of the radioactivity of the most radioactive node in the same anatomic area is considered an additional sentinel lymph node and is harvested separately. Relatively hot nodes in a different anatomic region that does not reach 10% of the radioactivity of the hottest node but has atleast 2 times radioactivity of the background readings must also be harvested as a sentinel node, as it may represent a separate drainage pattern from a different portion of the tumor.

Table 3A : Comparison between techniques for localization:

Study	No. of patients	SLN identified	True positive	False negative	Sensitivity (%)
Shoaib et al [35]	13-blue 13-radio	5 12	0 7	3 0	41 100
Civantos [65] (two) except blue	43	43	18	2	90
Stoeckli [67] (triple)	79	78	29	2	94
Ross [89] (triple)	134	125	42	3	93

Sentinel Lymph Node Biopsy – Drawbacks [48,49]:

The disadvantages of SLNB are

1. Skip metastasis alter management predictions.
2. Learning curve
3. Radionuclide retention in tissues.
4. Failure to identify sentinel nodes
5. Free soft tissue disease not taken into account

Frozen sections are unreliable to detect micro-metastasis and hence occult metastasis [50]. Sentinel lymph node biopsy is an acceptable procedure for microscopic disease; however clinical disease must be ruled out with clinical examination after induction of anesthesia.

For oral cancer, it appears that the sentinel node is an excellent tool for assessment of microscopic disease, but subclinical gross disease must be sought by radiologic studies and intraoperative palpation [51].

Sentinel Lymph Node Biopsy - Failure to Identify Sentinel Nodes: [52-53]

For T3 and T4 primary tumors difficulty in injecting the dye around tumor may alter the pickup rate requiring large volumes for these tumor, other reason for failure of SLNB technique include excessive uptake of radioactivity, potential for false-negatives caused by incomplete injection, and technical futility of removing a large number of nodes in piecemeal fashion. Bulky or deeply infiltrative primary tumors that invade adjacent anatomic subsites clearly pose technical difficulties for peritumoral injection.

Clinical node positivity predicts failure of the technique to identify sentinel node, hence anterior tongue and FOM are subsites with reduced success rate due to high risk of node positivity (20-30%).

FOM tumors lesions are the most difficult sub site for SLNB [53]. The lymph from the floor of mouth drains through nodes along lingual nerve (lingual nodes) to cervical nodes. Uptake in the lingual nodes and level I nodes overlap with the injection site uptake and SLNB may be missed. It is referred as the ‘‘shine through’’ phenomenon [53].

The mandible interferes with the gamma camera probe angulation. The technical difficulty may be overcome with several solutions like software masking, lead shields, removing the primary tumor prior to SLNB identification, and elective dissection of level I nodes can be useful but sentinel nodes for FOM remains problematic. Higher successful harvest rate is seen in patients with a positive

preoperative lymphoscintigraphy (94%) compared with patients with a negative preoperative lymphoscintigraphy (79%)

Delayed sentinel lymph node biopsy (D-SLNB) is defined as any SLNB procedure that is carried out after a previous wide local excision of the primary. A delay or more than 90 days, or cicatrix after Wide Local Excision alters lymph draining channels rendering the procedure unreliable and SLNB non-representative of the original lymphangiosome.

Sentinel Lymph Node Biopsy - Enhanced pathological review [54-60]:

A successful procedure relies on efficient screening by the pathologist. Extent to which SLNB upstages the neck by traditional pathologic methods seems to be similar to that with elective neck dissection. The use of additional pathologic methods results in perhaps an even greater level of detection of disease. The negative predictive value of frozen section ranges from 83 to 99% [55] depending on the slicing technique used and is higher for multi-slice technique [55]. Unlike frozen section, imprint cytology can also be used where concern about loss of tissue during processing does not exist [55].

Serial sectioning has to be done with more attention than usual. Tumor cells enter the node through the opposite side of hilum. SLNs less than 0.5 cm are processed entirely, nodes up to 1 cm are halved and sentinel lymph node more than 1cm are downsized to 0.5 cm and step sections are made if first section is negative. While cutting the step ribbons, one portion is retained for IHC and other for routine HPE staining [57]. Without step sections and immunohistochemistry, up to 15 to 20% of metastases may be missed [76]. Therefore, the theoretical sensitivity for detection of metastases by single HE frozen section analysis is (under optimal conditions) not

higher than 80 to 85% [58]. These small deposits of occult disease are likely to be overlooked by the routine histological assessment of the large number of nodes in a neck dissection specimen.

Sentinel Lymph Node Biopsy - Rapid Molecular Detection as an Intraoperative Adjunct [60]:

Frozen section results vary with pathologist and technical staff. Since sensitivity is not very high, molecular detection came in to practice for the last 2 years. It is quick, has high negative predictive value and facilitates one time surgery [60]. Use of qRT-PCR (Reverse Transcriptase associated Polymerase Chain Reaction) permits quick and reliable assessment and can be useful tool in decision making. Per operative molecular staging with PCR amplification of marker genes could spare 60-70% of pN0 patients from unnecessary surgery [60].

Sentinel Lymph Node Biopsy - Classification and Staging [61]:

UICC definitions of metastatic deposits divided into macrometastasis (>2 mm), micro metastasis (0.2-2 mm) and even small tumour cells or small clusters <0.2 mm (isolated tumour cells, ITC).

Generic TNM Coding For Sentinel Nodes	
pNX (sn)	Sentinel lymph node could not be assessed
pN0 (sn)	No sentinel node metastasis
pN1 (sn)	Sentinel node metastasis
Sentinel nodes with micrometastasis only are identified by (mi)	
pN1(sn) (mi)	Single ipsilateral node with micrometastasis
pN2 (sn) (mi)	Multiple ipsilateral nodes with micrometastasis.
Sentinel nodes with isolated tumour cells	
pN0 (i-)(sn)	No sentinel lymph node metastasis histologically, negative morphological findings for isolated tumour cells (ITC)
pN0 (i?)(sn)	No sentinel lymph node metastasis histologically, positive morphological findings for isolated tumour cells (ITC)
pN0 (mol-)(sn)	No sentinel lymph node metastasis histologically, negative non-morphological findings for isolated tumour cells (ITC)
pN0 mol?)(sn)	No sentinel lymph node metastasis histologically, positive non-morphological findings for isolated tumour cells (ITC

Sentinel Lymph Node Biopsy - Outcomes:

Three prospective studies and good quality of SLNB are in progress namely SENT [(62)], DAHANCA 22 [(63)], Brazilian Head & Neck Group [(64)]. Recently the prospective multi-institutional clinical trial by ACOSOG Head and Neck Committee has shown encouraging results [(65)]. The Efficacy of Sentinel Node Biopsy in Head and Neck Cancers in various studies are shown in Table 4.

Table 4 Efficacy of Sentinel Node Biopsy in Head and Neck Cancers

Author	No. of Patients (n)	SLNB Identification rate	NPV	Occult Metastases (n)
Ross et al (2005) [66]	134	125/134	96%	39 (33%)
Stoeckli et al.(2008) [67]	79	79/79	100%	26 (32%)
Alkusheri et al (2010) [68]	134	125/134	94.6%	42 (34%)
Melakane et al (2012) [69]	166	154/166	95.2%	42 (25%)
Antanio et al (2012) [70]	209	183/209	94.9%	54 (29.5%)

Sentinel Lymph Node Biopsy – the consensus in literature [71]:

1) Negative predictive value is between 90% and 100%.
2) Step serial sectioning and IHC are essential parts of the procedure.
3) IHC and step serial sectioning yields better results and significantly improve the negative predictive value of this technique.
4) Compared to Lymphadenectomy SLNB significantly upstages nodal stages.
5) Unexpected patterns of lymphatic drainage can indeed occur, including unanticipated contralateral drainage to nodes that might be missed in standard lymphadenectomy

6) Frozen section, imprint cytology, and molecular biology based technique permits quick and reliable assessment of nodes facilitating the neck dissection at the same sitting if appropriate.

Following are significant concerns. Staged surgery is required in a small group when positive nodes are found after formal processing at later date.

The best treatment of neck with single micro metastasis or even isolated tumor cells is elusive [72]. It has been proposed that removal of the sentinel node alone may be sufficient in these patients but without strong evidence [73].

Selective Neck Dissections and post-operative shoulder dysfunction syndrome:

Subclinical spinal accessory nerve impairment can be observed even after selective neck dissections (levels I-III) due to routine clearance of sublevel II B [74]. The most common morbidity associated with selective neck dissection (SND-I-III) is spinal accessory nerve dysfunction and related shoulder disability [75,76] . Nerve morbidity is mainly due to stretching while clearing level IIB nodes. If these nodes are not dissected the above mentioned morbidity can be prevented.

Even after careful dissection of the posterior triangle, unavoidable trauma to the accessory nerve (SAN) does occur. Potential reason for the nerve dysfunction includes traction injury, use of diathermy and vascular injury. Postoperative hemorrhage, infection and scarring may affect nerve function. Apart from injury to SAN, connections with the cervical plexus are damaged invariably during dissection of Level V. All these factors lead to shoulder syndrome. This syndrome is characterized by shoulder pain, weak abduction, and winging scapula. These symptoms may lead to significant restrictions in patient's professional and every day

activity [77]. Pinsolle et al (1997) [77] found in a series of 41 patients following supraomohyoid neck dissection, 32% to have minor, 5% moderate, and 2.5% severe shoulder problems. Paul van et al (2003) [78] in a study of 58 patients showed 14 (28%) shoulder dysfunction.

Is Level II B removal necessary?

Involvement of IIb nodes is rare in clinically N0 oral cavity cancers [79-82]. This has led to the idea of preserving them to avoid trauma to Spinal Accessory Nerve. This is anticipated to have a better functional out come and reduced morbidity [80, 81]. The review of literature (Table 5) suggests that metastatic involvement of level IIb is rare based on from both elective and therapeutic neck dissection.

Table 5 Involvement of Level IIB Nodes

Author	No. of Neck Dissections	Level IIb no. and (%)	Exclusive Level IIb involvement
Lim et al [2004]	74	4(6.7)	0
Elsheikh et al [2005] [79]	48	1(2)	1
Lim et al [2006] [80]	125	8(6.4)	0
Villaret et al [2007] [81]	43	26(5.6)	2
Manola et al 2011 [82]	34	0	0

It shows Level IIb involvement ranges between 2- 6.5% in cN0 neck. But in presence of clinically palpable nodes and level II involvement metastasis increase upto 22—36% [106]. Hence, routine clearance of IIb is not necessary in N0 neck.

Is Level IV and V clearance necessary? :

In clinically N0 neck of oral cavity cancers, level IV and V nodes are not first echelon nodes. Skip metastasis to level IV & V are rare. Shah JP *et al* (1990) [(83)] found that in oral cavity cancers occurrence of level IV metastases was 3% in N0 neck and 17% in node positive neck and the prevalence of neck metastases in level V is 0.5% in N0 and 3% in node positive. Davidson *et al* (1993) [(84)] in a review of 1123 patients who underwent a neck dissection for squamous cell carcinoma of the head and neck and reported a 3% incidence of histologically positive nodes at level V, with 1% for N0 and 5% for node positive patients.

Dissection of level IV is associated with two important complications injury to thoracic duct (left), and injury to phrenic nerve. Dissection of Level V can cause injury to spinal accessory nerve, transverse scapular vessels, cervical plexus and brachial nerve plexus. Dissection of level V area is also associated with shoulder dysfunction syndrome. Hence sparing these groups of lymph nodes in elective neck dissection of clinically negative neck can decrease the morbidity without compromising oncologic cure [(85)].

Rationale for the present study:

There is continuing debate over management of clinically negative neck. Since occult neck node metastases is about 30% there is high probability that neck can be under staged if only clinical examination is used to stage the neck. Imaging modalities like ultrasound CT scan and MRI have contributed in detecting metastatic nodes in clinically negative neck, but no imaging modality is capable of diagnosing micro-metastases in less than 5mm node.

Sentinel lymph node biopsy is a promising tool slowly gaining popularity in Head neck cancers. It is reasonably accurate in predicting nodal metastases. Apart from conventional histopathological techniques serial sectioning, routine use of immuno-histochemistry and more recently use of molecular markers have improved the detection of nodal metastases. Combination of these two tools may give even superior and accurate staging information.

MATERIAL AND METHODS

Study design:

This **prospective pilot study** was carried out in Department of Surgical oncology with collaboration of Department of pathology and Radiology, Government Royepettah Hospital, Chennai. Patients of oral cancer with clinically negative neck are included in the study, after obtaining informed consent. Thirty two patients with oral cancers with stages T1-T3, N0 were included in the study.

Inclusion criteria:

1. Patients with oral cancer clinically negative neck nodes.
2. Patients above 18 years age with ability to give consent.

Exclusion Criteria:

1. Patient with T4 tumour
2. Patients primarily treated by radiotherapy.
3. Patients who had previous surgery in neck.
3. Patients with palpable nodes.
4. Patients who are not medically fit to undergo surgery.
5. Histology other than Squamous cell carcinomas.
6. Patients not willing to participate in the study.

Clinical Evaluation:

Comprehensive history was taken and through clinical examination carried out. Details about age, sex, religion, any family history of head and neck cancer were recorded. History of tobacco chewing, pan, quid, smoking and alcohol were enquired. Symptoms like ulcer, pain bleeding, hyper salivation, etc. elaborated in detail. Oral cavity examined for any pre-malignant conditions like leukoplakia, sub-mucus fibrosis. Side, T stage of the tumor and type of tumor noted. Neck is examined for palpable lymph nodes. Only patients who were clinically negative for lymph nodes were taken in for the study.

Ultrasound Examination*:*

Ultrasound examination is done with real time scanner with probe head of 7.5 MHz frequency transducer. The neck is examined longitudinal and transversely in continuous sweep technique covering from the thoracic inlet to the sub mentum. If any found on ultrasound the level, size, echogenicity and other characteristics is noted.

Sentinel lymph node biopsy (SLNB):

Patients in the study were injected with 2 ml of methylene blue dye peritumorally at 3, 6, 9 and 12' clock position (0.5 ml in each quadrant) in the operating room after anesthesia. Stop clock is started to set the maximum limit as 20 minutes. Lymph nodes were harvested between 10 – 20 minutes and if dissection exceeds beyond 20 min, the patient was excluded from the study.

Neck incision is marked as per the convenience of surgeon (crile's, hemi-apron). Tumescent is injected along the marked incision and sub platysmal flaps are raised superiorly and inferiorly.

Then visual inspection of the draining area is done for the blue colored node, before removal of any lymphatic tissue. Any blue node found is dissected out separately and sent for Frozen & histopathological examination. If Lymph node has not taken the stain then blue stained lymphatics were sought and traced till the draining lymph node and the same node is treated as sentinel node. Presence or absence of blue nodes, number of nodes and the level of nodes were noted.

Selective neck dissection is completed from Level Ia, Ib, IIa, IIb, III, IV separately.

Frozen section and serial sections of the sentinel lymph node is prepared with hematoxylin and eosin stain and examined under microscope for macro or micro metastasis or isolated tumor cells. Immunohistochemistry using pancytokeratin marker was done at a later date to detect occult disease.

Neck dissection:

All patients are subjected to selective neck dissection. Lymph nodes are retrieved from all levels and sublevels separately. Lymph nodes are labeled as Level Ia, Level Ib, Level IIa, Level IIb, Level III, Level IV. Type of neck dissection, number of lymph nodes in each dissection is recorded. The number of lymph nodes from each level and sub level noted separately. Histopathological examination is done with routine hematoxylin and eosin staining. Involvement of Level IIb, Level IV was specifically recorded.

Postoperative Histopathology:

1) **Primary tumor:** Post-operative specimen of primary tumor is examined under hematoxylin and eosin stain after preparing paraffin sections. Tumor Grade,

margin, tumor thickness, vascular invasion, peri-neural invasion, Lymphatic invasion and muscle invasion are noted.

2) **Lymph nodes of neck**:

Number of nodes harvested at each level and sub-level is noted. Lymph nodes are examined after fixing and staining for metastasis, extra capsular spread.

Follow up:

All patients are followed up and advised adjuvant treatment as appropriate. They are examined regularly for any evidence of loco-regional and distant metastases monthly for the first 2 years, when there is highest chance of recurrence. For the next year every second monthly review is done.

Outcome Measures:

The primary outcome of the study was to analyze the feasibility of sentinel lymph node assisted selective neck dissections in clinically N0 patients using blue dye. The secondary outcome measures were- i) analyses the incidence and level of involvement of lymph nodes in carcinoma oral cavity. ii) Correlation with tumor stage and grade. iii) Comparison of accuracy of neck staging with SLNB to neck dissection. iv) Identification of factors predicting the node positivity in oral cavity cancers. v) Evaluation of the necessity of level IIB, IV clearance in neck dissections.

Table 6 Boundaries of Neck Dissection (ref- as defined by MSKCC group)

Boundaries				
Level	**Superior**	**Inferior**	**Anterior (medial)**	**Posterior (lateral)**
IA	Symphysis of mandible	Body of hyoid	Anterior belly of contralateral digastrics muscle	Anterior belly of ipsilateral digastrics muscle
IB	Body of mandible	Posterior belly of muscle	Anterior belly of digastrics muscle	Stylohyoid muscle
IIA	Skull base	Horizontal plane defined by the inferior body of the hyoid bone	Stylohyoid muscle	Vertical plane defined by the spinal accessory nerve
IIB	Skull base	Horizontal plane defined by the inferior body of the hyoid bone	Vertical plane defined by the spinal accessory nerve	Lateral border of the sternocleidomastoid muscle
III	Horizontal plane defined by inferior body of hyoid	Horizontal plane defined by inferior border of cricoid cartilage	Lateral border of the sternohyoid muscle	Lateral border of sternocleidomastoid or sensory branches of cervical plexus
IV	Horizontal plane defined by the inferior border of cricoid cartilage	Clavicle	Lateral border of the sternohyoid muscle	Lateral border of the sternocleidomastoid or sensory branches of cervical plexus
VA	Apex of the convergence of the sternocleido mastoid and trapezius muscles	Horizontal plane defined by the lower border of the cricoid cartilage	Posterior border of sternocleido mastoid muscle or sensory branches of cervical plexus	Anterior border of the trapezius muscle
VB	Horizontal plane defined by the lower border of the cricoid cartilage	Clavicle	Posterior border of sternocleido mastoid muscle or sensory branches of cervical plexus	Anterior border of the trapezius muscle
VI	Hyoid bone	Suprasternal	Common carotid artery	Common carotid artery

STATISTICAL ANALYSIS

Statistical analysis was done with SPSS for Windows, 16.0 version (® SPSS Inc, USA). Quantitative data are described as mean and standard deviations. Categorical data are shown as Proportions. Data are also presented graphically with bar diagrams and pie charts. Data were explored for any outliers, typing errors and missing values. Comparison of groups was carried out for various categorical variables using Chi-square test of association. A p-value (two-tailed) < 0.05 was taken as significant.

RESULTS AND OBSERVATIONS

In our study of 32 patients of whom 24 (75%) were male and 8(25%) with mean age 43 (26-70) years, right (n=16) and left (n=16) sided tumor were equal. Clinical Tumour status T1, T2 and T3 in this study were 16 (50%), 14 (43.7%), 2 (6.3%) respectively. 19 (59.7%) patients were smokers, 10 (31.2%) were alcoholic, 9(28%) patients used tobacco quid and others forms tobacco usage occurred in7 (21%) (Table 7)

Table 7: General Patient Characteristics

General Patient characteristics:		**No. of patients**	**Percentage**
Age distribution 26-70 (mean 43 years)	Less than 50 years	14	43.8%
	50 years & above	18	56.3%
Sex distribution	Male	24	75%
	Female	8	25%
Addictions	Smoking(cigar, beedi)	19	59.4%
	Smokeless tobacco	16	50 %
	Alcohol	10	31.3%
Laterality	Left	16	50%
	Right	16	50%
Clinical tumour staging	T1	16	50.0%
	T2	14	43.8%
	T3	2	6.3%

Tongue was the most common site involved in a 18 (56%), followed by buccal mucosa 7 (22%) then hard palate 2(6%), retro-molar trigone 2(6%), hard palate 2 (6%) floor of mouth 1(3%) (Figure-4) Morphologically ulcero-proliferative type is the most common occurring in 16 (50%) patients and other types include ulcerative, infiltrative and verrucous type in 8 (25%), 6 (18.8%), 2 (6.3%) respectively (figure-5).

Symptoms like ulcer occurred in 18 (56.3%) patients, or ulcer with pain 12(37.5%), hyper salivation, difficulty in swallowing and referred otalgia are less common mode of presentation in our early tumors (one patient each) (figure-6). Patients presented within and after 4 months were 21 (65.6%) and 11 (34.4%) respectively. Earliest reported was 15 days and longest was 11 months. Correlation of duration with T stage and grade was not significant (table 8 and 9)

Table 8 Duration of Symptoms vs. T stage

Duration	**T1**(n=16)	**T2**(n=14)	**T3**(n=2)	**Total**(n=32)
2 months or less	2 (50%)	2 (50%)	0	**4**
3-4 months	10 (58.8%)	6 (35.3%)	1 (5.9%)	**17**
More than 4 months	4 (36.4%)	6 (54.5%)	1 (9.1%)	**11**
Total	**16**	**14**	**2**	**32**

Chi-square value: 1.934; P= 0.748

Figure 4: Tumour Subsite

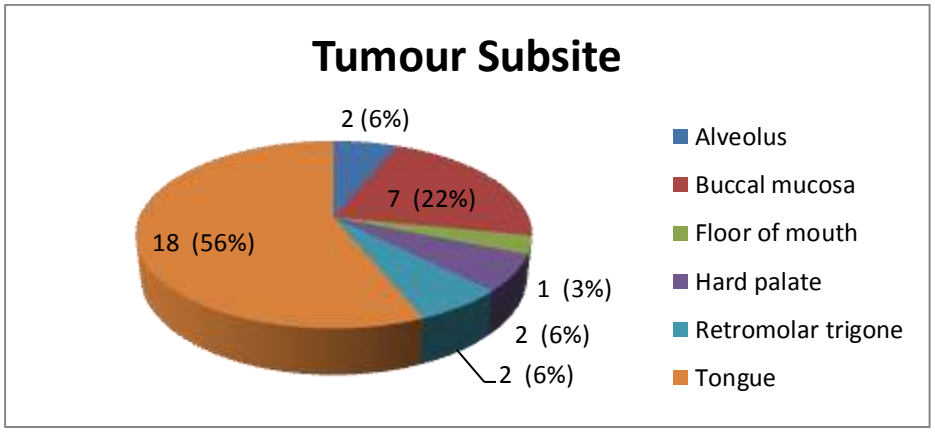


Figure 5: Morphology of Tumour

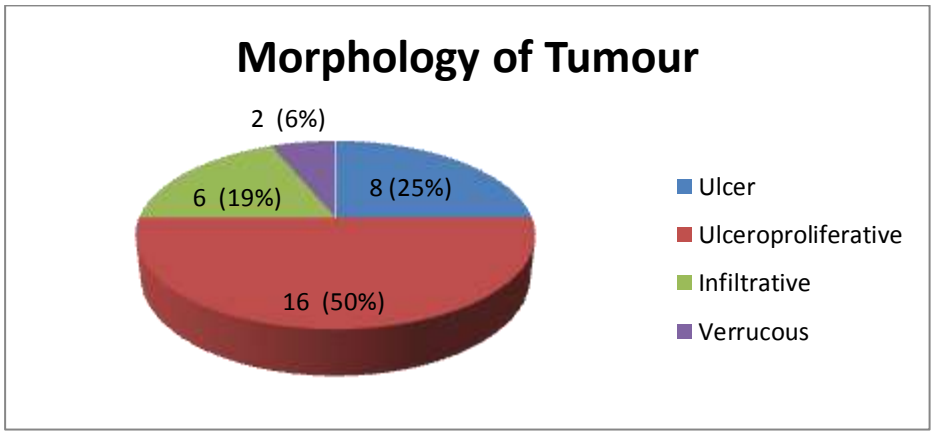
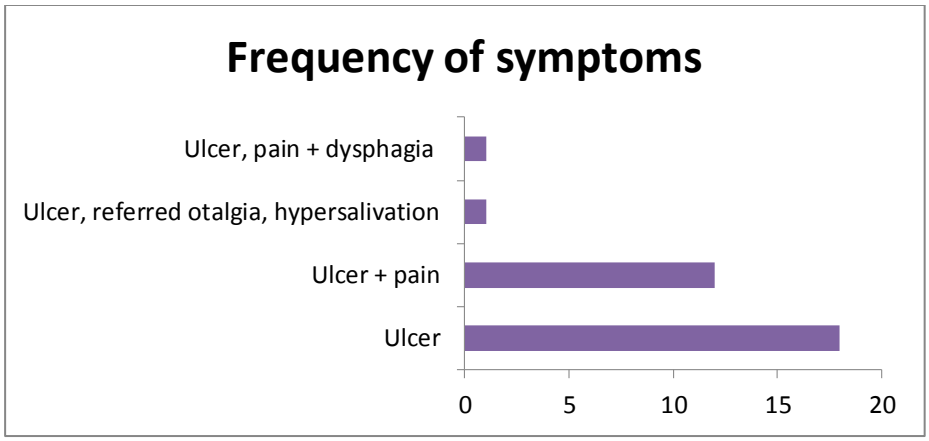


Figure 6: Frequency of symptoms



Nineteen patients (59.3%) had well differentiated, 12(37.5%) moderately differentiated and 1(3.2%) poorly differentiated tumours. Correlation of grade with T stage and duration of symptoms was not significant (table9 and 10).

Table 9 Duration of Symptoms vs. Grade of tumour

Duration	**Grade 1**	**Grade 2**	**Grade 3**	**Total**
2 months or less	2 (50%)	2 (50%)	0	**4**
3-4 months	11 (64.7%)	6 (35.3%)	0	**17**
More than 4 months	6 (54.5%)	4 (36.4%)	1 (9.1%)	**11**
Total	**19**	**12**	**1**	**32**

Chi-square value: 1.666; P= 0.435

Table 10 Grade of tumour Vs Pathological tumour staging

Grade of tumour	**Pathological tumour staging**			**Total**
	T1	**T2**	**T3**	
Grade 1	12 (63.2%)	5 (26.3%)	2 (10.5%)	**19**
Grade 2	4 (33.3%)	8 (66.7%)	0	**12**
Grade 3	1 (100%)	0	0	**1**
Total	**17 (53.1%)**	**13 (40.6%)**	**2 (6.3%)**	**32**

Chi-square value: 7.356 (P=0.118)

Correlation with the smoking with subsite, stage and grade of tumor (table 11,12,13) has revealed smokers found to have carcinoma tongue twice likely than nonsmokers. Floor of mouth and retromolar tumors occurred exclusively in smokers and alveolus and hard palate in nonsmokers only. Correlation of smoking with T stage and grade was not significant (table 12 and 13)

Table 11 Sub-site distribution among smokers & non smokers

Site	Smoker	Non- smoker	Total
Alveolus	0	2 (100%)	**2**
Buccal mucosa	4 (57.1%)	3 (42.9%)	**7**
Floor of mouth	1 (100%)	0	**1**
Hard palate	0	2 (100%)	**2**
RMT	2 (100%)	0	**2**
tongue	12 (66.7%)	6 (33.3%)	**18**
Total	**19 (59.4%)**	**13 (40.6%)**	**32**

Chi-square value: 10.754; P= 0.056

Table 12 Smoking Vs. tumour staging

Smoking habit	Pathological tumour staging			Total
	T1	T2	T3	
Non smoker	8 (61.5%)	4 (30.8%)	1 (7.7%)	**13**
Smoker	9 (47.4%)	9 (47.4%)	1 (5.3%)	**19**
Total	**17 (53.1%)**	**13 (40.6%)**	**2 (6.3%)**	**32**

Chi-square value: 0.901 (P=0.924)

Table 13 Grade Vs Smoking

Smoking status	Grade 1	Grade 2	Grade 3	Total
Smoker	10 (52.6%)	8 (42.1%)	1 (5.3%)	19
Non-smoker	9 (69.2%)	4 (30.8%)	0	13
Total	19	12	1	32

Chi-square value: 1.666; P= 0.435

Alcoholic and tobacco users were analysed for any significant correlation between "T" status and grade none were statistically significant **(Tables** 14, 15).

Table 14 Alcohol Vs tumour staging

Alcohol intake	**Pathological tumour staging**			**Total**
	T1	**T2**	**T3**	
Non alcoholic	13 (59.1%)	8 (36.4%)	1 (4.5%)	**22**
Alcoholic	4 (40%)	5 (50%)	1 (10%)	**10**
Total	**17 (53.1%)**	**13 (40.6%)**	**2 (6.3%)**	**32**

Chi-square value: 1.103 (P=0.576)

Table 15: Smokeless Tobacco usage Vs tumour staging

Tobacco usage	**Pathological tumour staging**			**Total**
	T1	**T2**	**T3**	
Non tobacco user	10 (43.5%)	11 (47.8%)	2 (8.7%)	**23**
Smokeless Tobacco User	7 (77.8%)	2 (22.2%)	0	**9**
Total	**17 (53.1%)**	**13 (40.6%)**	**2 (6.3%)**	**32**

Chi-square value: 3.827 (P=0.148)

Table 16: Distribution of addictions

Addictions	**Frequency**	**Percentage**
No addiction	7	21.9%
Smoker (or) Alchol (or) smokeless tobacco	11	34.4%
Any 2 addictions	8	25%
All 3 addictions	6	18.8%
Total	**32**	**100%**

Overview of Sentinel Lymph Node Biopsy

In 29 SLNB identified neck dissections, 50 sentinel nodes were harvested with mean 1.56 nodes.

Table 17: Overview of Sentinel Lymph Node Biopsy

Total No. of patients	32
No. of patients from whom SLN were harvested	29
Sentinel lymph node localization rate	90.6%
No. of patients in whom SLN was positive by Frozen section	5
No. of false positive by Frozen section	1
No. of false negative by Frozen section	1
No. of patients in whom nodes were positive by enhanced pathological review	1
No. of patients in whom nodes were positive by Cytokeratin	3

There is considerable variation in the mean number of sentinel node harvest with retromolar trigone having the highest yield 2.5 per patient hardpalate has least with 1 node per patient. Distribution of total number sentinel lymphnode dissected in hard palate, buccal mucosa, tongue, alveolus, floor of mouth and RMT were (2, 9, 28, 4, 2, 5) and mean is (1, 1.28, 1.56, 2, 2, 2.5) respectively (table 17,18).

Out of 8 positive nodes, level IB was positive in two patients, IIA positive in four patients and Level III was positive in two patients. In the five positive neck 3 nodes(IB, IIA,III) were harvested in one patient, two patients with two nodes (IIA,III & IB,IIA) and two patients has one node each in IIA level. In these patients except two node patients (IIA, III) who had only level III positive, all the other patients had

all sentinel nodes were positive. In the positive neck patient out of 9 nodes harvested 8 were positive for occult metastasis (table 19).

Table 18: Distribution of tumour and sentinel nodes

Site of tumour	No. of patients	No. of SLN dissected	Mean no. of nodes per patient
Alveolus	2	4	2
Buccal mucosa	7	9	1.28
FOM	1	2	2
Hardpalate	2	2	1
RMT	2	5	2.5
Tongue	18	28	1.56
Total	**32**	**50**	**1.56**

Table 19: Analysis of 5 SLNB positive patients

S NO	Level of SLNB	No of positivity
1	IB,IIA,III	IB, IIA, III positive
2	IIA	IIA positive
3	IIA, III	III positive
4	IB,IIA	IB,IIA positive
5	IIA	IIA positive

When analyzing the factors affecting the nodal positivity all the 5 positive patients were carcinoma tongue. Patients with T1, T2 were involved in 3 (21.4%), 2 (15.4%). Well, moderately, poorly differentiated were involved in 3 (17.6%), 1 (9.1%), 1 (100%) respectively. None of factors were found to have statistically significant (table-20).

Table 20: Factors affecting sentinel node positivity

Patient characteristics		**Sentinel node frozen section**		**Total**	**significance**
		Positive	**Negative**		
Site of tumour	Non tongue	0	13 (100%)	13	**P=0.029**
	Tongue	5 (31.2%)	11 (68.8%)	16	
	Total	**5 (17.2%)**	**24 (82.8%)**	29	
Duration	2 months or less	1 (33.3%)	2 (66.7%)	3	**P= 0.678**
	3-4 months	2 (12.5%)	14 (87.5%)	16	
	>4 months	2 (20%)	8 (80%)	10	
	Total	**5 (17.2%)**	**24 (82.8%)**	29	
"T" status	T1	3 (21.4%)	11 (78.6%)	14	**P= 0.621**
	T2	2 (15.4%)	11 (84.6%)	13	
	T3	0	2 (100%)	2	
	Total	**5 (17.2%)**	**24 (82.8%)**	29	
Grade	Grade 1	3 (17.6%)	14 (82.4%)	17	**P= 0.128**
	Grade 2	1 (9.1%)	10 (90.9%)	11	
	Grade 3	1 (100%)	0	1	
	Total	**5 (17.2%)**	**24 (82.8%)**	29	

FACTORS AFFECTING SENTINEL NODE IDENTIFICATION:

Sentinel lymph node localization rate 90.6% and 3 patients who were not identified are >50 years and male. Tongue, T1 tumors and well differentiated tumors were the factors for non-identification in two out of three patients (table 21).

Table 21: Factors Affecting Sentinel Node Identification

Patient Characteristics		**Sentinel node status**		**Total**	**P Value**
		Identified	**Not identified**		
Age group	< 50 years	14 (100%)	0	**14**	0.114
	≥50 years	15 (83.3%)	3 (16.7%)	**18**	
	Total	**29 (90.6%)**	**3 (9.4%)**	**32**	
Sex	Male	21 (87.5%)	3 (12.5%)	24	0.555
	Female	8 (100%)	0	8	
	Total	**29 (90.6%)**	**3 (9.4%)**	**32**	
Subsite	Alveolus	2	0	2	0.9
	Buccal mucosa	6 (85.7%)	1 (14.3%)	7	
	FOM	1	0	1	
	Hardpalate	2	0	2	
	RMT	2	0	2	
	Tongue	16 (88.9%)	2 (11.1%)	18	
	Total	**29 (90.6%)**	**3 (9.4%)**	**32**	
Tumour Stage	T1	14	2	16	0.722
	T2	13	1	14	
	T3	2	0	2	
	Total	**29 (90.6%)**	**3 (9.4%)**	**32**	
Grade of tumour	Grade 1	17 (89.5%)	2 (10.5%)	19	0.886
	Grade 2	11 (91.7%)	1 (8.3%)	2	
	Grade 3	1 (100%)	0	1	
	Total	**29 (90.6%)**	**3 (9.4%)**	**32**	

Sentinel lymphnode commonly harvested in level IIA and IB next common sites include level III and IA. In level IIB and IV none of the SLNB was identified. In 32 neck dissections 13 (1.8%) nodes were positive out of 707 (mean 22) nodes harvested with maximum yield of nodes in level III and IIA.

Table 22: Distribution of metastasis in the neck dissection

Level	Total no. of LN harvested	Mean no. of LN harvested	LN's positive on HPE	Distribution of Sentinel node
Ia	89	2.78 (0-6)	0	4
IB	104	3.25 (1-8)	4	20
IIa	145	4.53 (2-10)	6	21
IIB	98	3.06 (1-6)	0	0
III	149	4.66 (1-12)	3	5
IV	114	3.56 (0-12)	0	0
V	22	4.4 (0-6)	0	0
Total	707	22.09	13	50

When analyzing the factors contributing to nodal positivity it was found all were non tobacco users. Non alcoholic and non smokers are at high risk than alcoholic and smokers (3 vs 2). Comparing the "T" status T1, T2, and grade 1, 2, 3 were involved in 12.5%, 21.4%, 10.5%, 16.7%, and 100% respectively. However none of the factors turned out to be significant enough to make a difference.

FACTORS AFFECTING PATHOLOGICAL NODE POSITIVITY

Table 23: Factors affecting pathological node positivity

Patient Characteristics		**Pathological node status**		**Total**	**P Value**
		Positive	**Negative**		
Tobacco usage	Non tobacco user	5 (21.7%)	18 (78.3%)	23	0.134
	Tobacco user	0	9 (100%)	9	
	Total	**5 (15.6%)**	**27 (84.4%)**	**32**	
Smoking	Non smoker	3 (23.1%)	10 (76.9%)	13	0.345
	Smoker	2 (10.5%)	17 (89.5%)	19	
	Total	5 (15.6%)	27 (84.4%)	32	
Alcohol intake	Non alcoholic	3 (13.6%)	19 (86.4%)	22	0.651
	Alcoholic	2 (20%)	8 (80%)	10	
	Total	**5 (15.6%)**	**27 (84.4%)**	**32**	
Tumour Stage	T1	2 (12.5%)	14 (87.5%)	16	0.568
	T2	3 (21.4%)	11 (78.6%)	14	
	T3	0	2 (100%)	2	
	Total	**5 (15.6%)**	**27 (84.4%)**	**32**	
Grade	Grade 1	2 (10.5%)	17 (89.5%)	19	P=0.126
	Grade 2	2 (16.7%)	10 (83.3%)	12	
	Grade 3	1 (100%)	0	1	
	Total	**5 (15.6%)**	**27 (84.4%)**	**32**	

Immunohistochemistry using Pan-Cytokeratin analysis showed 8 out of 29 were positive (figure-7). This protocol sentinel node assisted neck dissection

converted 5 patients to MRND-1 out of 32 patients (figure - 8). Surgical procedures performed in this study were enumerated in the diagram (figure - 9). Out 14patients who underwent reconstruction are as in (figure- 10). Post treatment adjuvant treatments given to these patients were as in (figure - 11).

Out of 32 patients 8(25%) patients harbor metastasis in the lymphnodes. These patients were upstaged, considering the factors affecting stage migration, stage subsite were taken into account. Of these factors increasing "T' status increases chance of migration T1 vs T3 (25% vs 50%). Tongue is the most common site to be upstaged and followed by alveolus and buccal mucosa. Among the grade of lesion poorly differentiated tumours were upstaged commonly rather than well differentiated tumours (100% vs 31%). (Table 24)

Figure -7: Cytokeratin analysis of sentinel nodes:

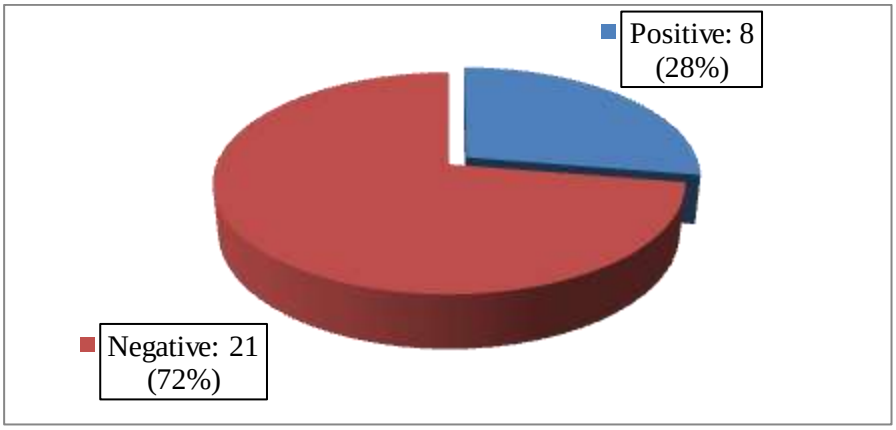


Figure – 8: Types of neck dissection performed:

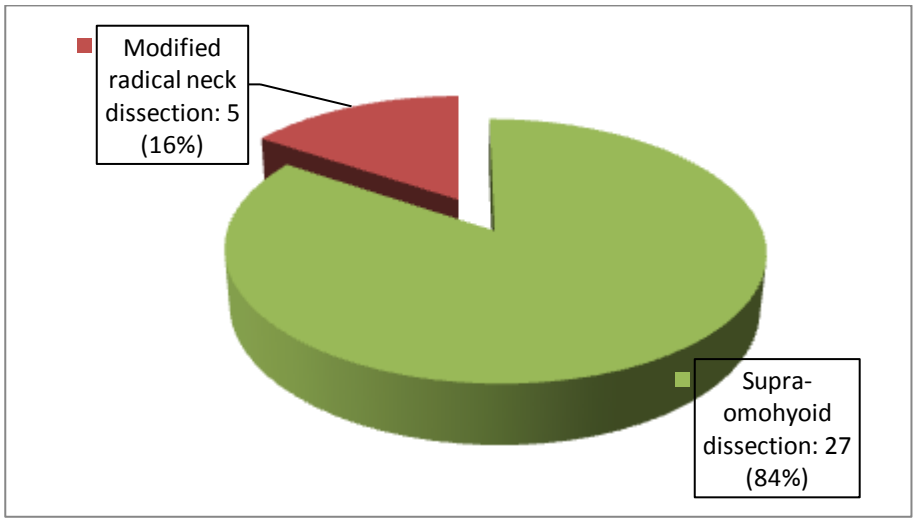


Figure -9: Types of procedure performed

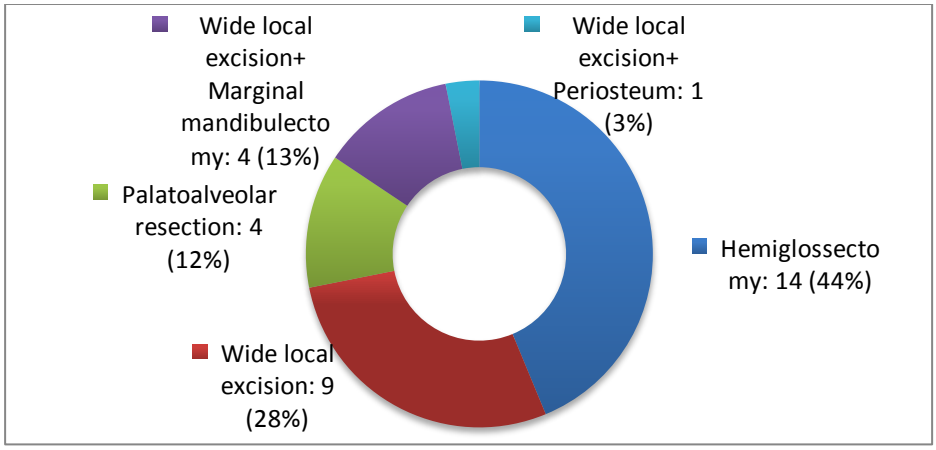


Figure- 10: Reconstruction n= 14

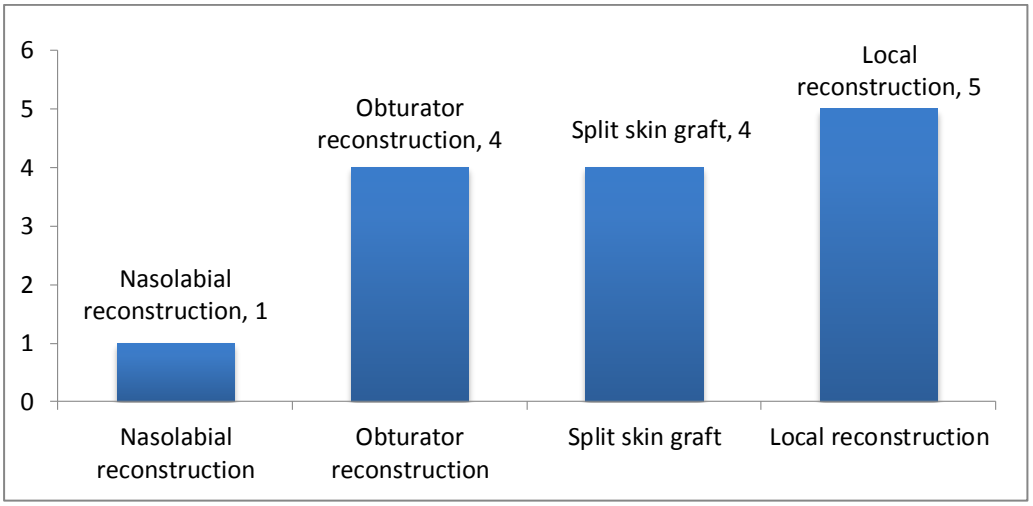


Figure -11: Adjuvant treatment in 32 patients:

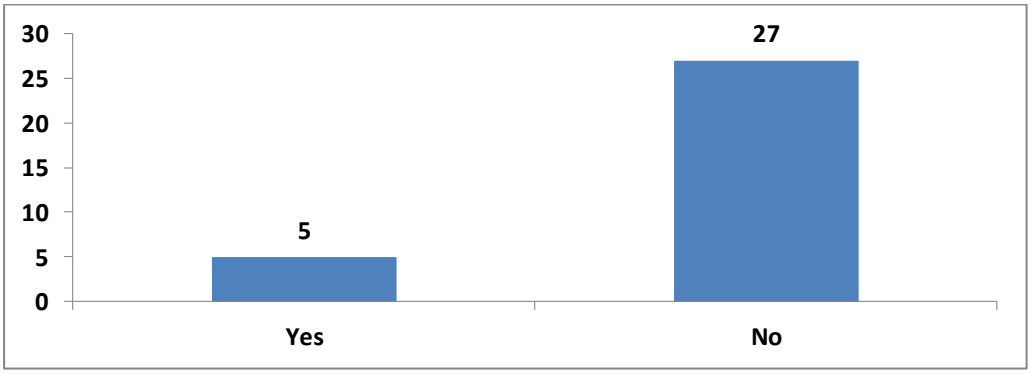


Table 24: Factors affecting Stage migration

Patient characteristics		N	Frozen	HPE	Cytokeratin
Clinical Stage	T1	16	3 (18.8%)	2 (12.5%)	4 (25%)
	T2	14	2 (14.3%)	3 (21.4%)	3 (21.4%)
	T3	2	0	0	1 (50%)
Subsite	RMT	2	0	0	0
	FOM	1	0	0	0
	Alveolus	2	0	0	1 (50%)
	Hardpalate	2	0	0	0
	Buccal mucosa	7	0	1 (14.3%)	1 (14.3%)
	Tongue	18	5 (27.8%)	4 (22.2%)	6 (33.3%)
Grade	Grade 1	19	3 (15.8%)	2 (10.5%)	6 (31.3%)
	Grade 2	12	1 (8.3%)	2 (16.7%)	1 (8.3%)
	Grade 3	1	1 (100%)	1 (100%)	1 (100%)

EVALUATION OF FROZEN SECTION OF SLN AS A SCREENING TEST:

Table 25: Lymph node positivity based on technique

Nodal identification technique	SLN identified n=29		SLN Non identification n=3
	Positive	Negative	
Frozen section (n=29)	5	24	00
HPE (n=32)	4	1	negative
Cytokeratin (n=32)	4	4	negative

Out of 32 patients sentinel lymphnode identified in 29 patients using frozen section, which on later date using serial section and study found one false positive and false negative which was confirmed by cytokeratin in addition to three patients with metastasis. When frozen, HPE and cytokeratin were used as screening test its sensitivity, specificity, false negative, false positive, positive predictive value and negative predictive value as given in tables 26, 27.28

Table26: Frozen section positivity Vs Pathological node status

Frozen section SLN	**pN Status**		**Total**	**Efficacy of frozen section**	
	Positive	**Negative**			
Positive	4	1	5	Sensitivity: 80%	PPV: 80%
Negative	1	23	24	Specificity: 95.8%	NPV: 95.8%
Total	5	24	29	False (+) : 4.2%	False (-) : 20%

Table 27: Frozen section of SLN Vs Cyokeratin positivity

Frozen section SLN	**Cytokeratin**		**Total**	**Efficacy of Cyokeratin**	
	Positive	**Negative**			
Positive	4	1	5	Sensitivity: 50%	PPV: 80%
Negative	4	20	24	Specificity: 95.2%	NPV: 83.3%
Total	8	21	29	False (+) : 4.8%	False (-) : 50%

Table 28: Evaluation of HPE (Pn) against Cytokeratins

HPE	**Cytokeratin results**		**Total**	**Efficacy of** HPE	
	Positive	**Negative**			
Positive	4	1	**5**	Sensitivity: 50%	PPV: 80%
Negative	4	20	**24**	Specificity: 95.2%	NPV: 83.3%
Total	8	21	**29**	False (+) : 4.8%	False (-) : 50%

Sensitivity of sentinel node biopsy of using frozen section was 80% and specificity of 95.8% with negative predictive value of 95.8% when enhanced pathological review are considered as standard.

DISCUSSION

We conducted a pilot study to evaluate the feasibility and efficacy of sentinel lymph node assisted neck dissection using methylene blue dye in clinically node negative early stage oral cavity cancers at Government Royapettah Hospital. The results were as follows

Patient Demographics:

Age & sex: In our study, we had 32 patients of whom 24 (75%) were male and 8(25%) were female. The age distribution is 26-70 (mean 43 years). Stoeckli [(86)] et al studied 79 patients the mean age was 57 years. The male: female ratio was 53:26. Agarwal [(87)]et al (2011) in their study of 111 patients presenting with oral cavity cancer,90 (81%) were male and 21 (19%) were female.

Our patients were 10 years younger than what is reported in literature.

Site & distribution: In the present study, tongue was the most common site involved in 18(56.3%), followed by buccal mucosa 7 (21.9%) hard palate, retro-molar trigone, RMT and the least common is the floor of mouth. In a study by Stoeckli [(86)] et al oral tongue was the most common subsite and buccal mucosa was the least common subsite. Shenoi [(88)] et al reported in 2012 the buccal mucosa subsite distribution as 23.73%, mandibular alveolus 45.76%, tongue 18.31%, lips 3.05%, FOM 2.03% and palate 1.36%. Agarwal [(87)] et al (2011) in their 111 patient's found to be buccal mucosa (41%) to be the commonest.

In contrast to literature of western world where buccal mucosa is the least common which forms the second most common sub site in our population probably due to increased use of non-smoke tobacco products.

T status & grade: Stoeckli [86] et al studied 79 patients with early stage T1&T2 oral cavity squamous cell cancer without clinical and radiological evidence of cervical lymph nodes. One hundred and eleven patients studied by Agarwal [87] et al 51 each (46%) were well differentiated and moderately differentiated, whereas, 9 (8%) were poorly differentiated cancers 39%) presented with early stage disease (i.e. stage I and II).

In our study clinical Tumour status among our patients was T1-16 (50%), T2-14 (43.7%), and T3-2 (6.3%). Well differentiated, moderately differentiated and poorly differentiated occurred in 19(59.3%), 12(37.5%), 1(3.2%) respectively which is consistent with the reported literature. Distribution of grade was in par with literature however most of our patients presented with advanced stage. In early stage T1 and T2 were in equal distribution.

Patient Presentation:

Duration & symptoms: Shoenoi [88] et al 2012 showed 68.14% presented within 6 months and ulcer with mass is the most common presenting symptom**.** In another study by Agarwal [87] et al (2011) the most common presenting symptom was a mass/ulcer in the oral cavity, followed by pain, dysphagia and trismus.

In this study 17 (53.12%) patients had 3-4 month of symptoms before they sought medical attention and 4 (12.5%) presented within two months, however 11 (34.38%) patients reported after >4 months of symptoms Most of our patients presented with ulcer 18 (56.3%), followed by ulcer with pain 12(37.5%). Other symptoms like hyper salivation, difficulty in swallowing and referred otalgia were less common

Morphology: In Agarwal [87] et al's 111 patient's tumour mass was exophytic/ proliferative in appearance in 99 patients and ulcerative/infiltrative in the rest.

In our study Ulcero-proliferative type of growth was the most common morphology observed in 16 (50%) patients and the other types ulcerative, infiltrative and verrucous seen in 8 (25%), 6 (18.8%) and 2 (6.3%) respectively. Right and left sided lesions were in equal distribution.

Risk factors:

Major risk factor includes tobacco chewing, smoking and alcohol intake alone or in combinations and viral infection have been implicated in head and neck carcinogenesis.

Single vs. multiple: Shenoi [88] et al (2012) reported tobacco chewing alone in 31.86%, smoking alone in 15.93% and alcohol alone in 5.42%. Tobacco chewing with smoking or alcohol occurred in 18.6% and 7.12% respectively, all the three occurred in 15.93%. A wide variety of tobacco habits like smoking, chewing, snuffing, using burnt tobacco as powder or paste are prevalent in India, which is more so in the rural population than in their urban counterparts (National Sample Survey Organization, 1998). Smoking is most common form of tobacco consumption among males and smokeless tobacco among females (National Sample Survey Organization, 1998). The same Survey has shown that the tobacco consumption has decreased in both urban and rural males and females over the period 1987-94. Contrary to the popular belief that the tobacco consumption is increasing, this data shows that it has decreased in all sectors.

In our study 19 patients were smokers, 10 were alcoholic and 9 patients used tobacco quid. 21.9% of our patient did not have any addiction. In this study 34.4%,

25%, 18.8% were addicted to one, two and all the three habits respectively. Carcinoma of oral tongue was the most common cancer among the smokers (67% p= 0.056) in our study. However alcohol, tobacco quid or other addictions did not reach significance level as causative agent in our study.

Non-invasive imaging:

Imaging modalities which rely on morphological parameters like Ultrasound and CT scan have been used in detecting metastasis with varying results [(24-27)]. Debate persists over relative merits of imaging in evaluation of N0 neck [(24-27).] Studies that correlate radiological and histopathological findings show that early microscopic metastasis can be present in lymphnode smaller than 10mm. These nodes do not show central necrosis or extracapsular disease. We used ultrasound of the neck in all our patients before they were subjected to SLNB. The ultrasound of neck was not able to identify any metastatic node in the study patient.

Sentinel lymphnode biopsy:

Identification rate, factors affecting them: In a Multi- Institutional Prospective Study, Ross [(89)] et al reviewed the data from 22 centers and 316 patients with clinically N0 neck. The SLNB identification rate was 95% with a overall sensitivity of 90%. The sensitivity increased to 94% after exclusion of data from low volume centers (<10 patients). Alkureishi [(90)] reported an identification rate of (93%, 125/134 patients), with lower rates for FOM (88% vs. 96%, P = 0.14). Overall detection rates for sentinel neck nodes are greater than 95% and there is also a negative predictive value of 95% for SLNB[(91,92)].

In our study, 29 (90.6%) patients sentinel lymphnode were identified and in three patients (9.4%) sentinel nodes could not be demonstrated which is low compared to reported literature. All the 3 patients were males above 50 years. Two out of three where T1, well differentiated and tongue tumor.

Sentinel node positivity: Out of 32 neck dissection, 50 sentinel nodes was harvested with a mean of 1.56 nodes which is less than that reported in literature. In the 50 harvested nodes 8 (16%) showed metastasis. Out of 29 patients, 5 patients (17.2%) were positive for occult metastasis on frozen section. On further histopathological evaluation using step sectioning, one was false positive and the other was false negative. Three patients (10.3%) found to have micro metastasis using cytokeratin after histology reported benign disease. Out of 5 positive samples, level IB showed sentinel node in 2 patients, level IIA positive in 4 patients and Level III in two patients. Three level of nodes(IB, IIA,III) were harvested in one patient, two level of nodes in two patients (IIA,III & IB,IIA) and the next two patients had one node each in IIA level. When tumor stage and grade were compared no significant correlation could be seen (table-20).

Stage migration: In study by Alkureishi [(90)] et al 42 patients were upstaged by SNB (34%), with 10 patients having micro metastatic disease detectable only by SSS (n = 2) or IHC (n = 8).

In our study 8 out 32 patients (25 %) where upstaged using enhanced pathological review and IHC. T1 tumors (25%) and T3 tumors (50%) likely to undergo stage migration. Carcinoma tongue is the most common site to be upstaged; others include alveolus and buccal mucosa. Poorly differentiated tumors as compared to well differentiated tumors are more likely to undergo stage migration.

Intra-operative Frozen section Vs. Enhanced Pathological review Vs. IHC:

Serial sectioning, immunohistochemistry (IHC), and reverse transcriptase polymerase chain reaction (RT-PCR) may identify metastases missed by standard processing [(73-80)]. Although intraoperative frozen section has been evaluated for SNB, its sensitivity is not very high (60%), and an inherent problem with intraoperative frozen section is sampling error, because even one or two 5-mm frozen sections of a 1-cm LN only corresponds to 0.1%, which is visually analyzed and therefore may miss metastasis[(73-80)]. This is particularly true if the metastatic deposit is located near the capsule, as opposed to the mid-portion when the node is bivalved into two sections. Frozen-section histology is also subject to technical difficulties in sample and section preparation, including interpretive challenges, all of which are heavily dependent on the skill and experience of the pathologist and support staff. Even though final assessment of step-sectioned formalin-fixed, paraffin embedded sections is the gold standard and samples a larger percentage of the node. It can underestimate the tumor burden because it may not find micro metastatic deposits (<2 mm and >0.2 mm), and ITCs (tumor clusters <0.2 mm). This fact is indirectly suggested by "7% to 10% of pN0 patients after END experience recurrent disease in the neck". Hence, a method of evaluating a large portion of SLN for metastasis that is both rapid and accurate would be of great benefit.

Sensitivity of sentinel node biopsy of using frozen section was 80% and specificity of 95.8% with negative predictive value of 95.8% when enhanced pathological review is considered as standard. However if micro-metastasis are identified using IHC was considered as standard Frozen section sensitivity drops to 50% but has specificity 95.2 % and negative predictive value was 83.3%. In the 3

patients whom SLN were not identifiable, routine histopathological examination of the extended supra-omohyoid specimen were negative as well. In our study we had one false positive (Frozen positive HPE Negative) and one false Negative patient (Frozen negative, HPE Negative). Cytokeratin analysis revealed additional 3 patients harboring micro metastases in the sentinel node which was not detected by frozen section and enhanced pathological review.

Differential spread of tumors:

Several forms of differential tumor spread to lymphatics have been documented. In overflow phenomenon, advanced metastatic burden in first echelon nodes, resulting in embolic spread to lower anatomical levels to create inverted cone effect. . Fast tract nodes are those in which have primary drainage to level III and IV rather than upper levels. Peppering is isolated tumour cell(s)/ micro metastasis in nodes at multiple levels in the absence of macro metastasis. Soft tissue deposit is defined as metastasis with in area of lymphatic drainage but without any obvious nodal structure. Extracapsular disease occurring in the lymphnode can be macroscopic, microscopic and early microscopic.

In the study by Byers et al [(93)] 15.8% had either level IV metastasis as the only manifestation of disease in the neck or the level III node was the only node present without disease in level I-II. Skip metastases occur in carcinoma tongue and FOM which has been supported by anatomical studies [(94)]. Based on this extended supraomohyoid dissection became treatment of choice [(93,94).]

In our study we did not have any skip metastasis, extracapsular disease and soft tissue deposit or overflow phenomenon. Peppering of nodes occurred in 2/5 (40%) patients. Fast tract node occurred in one patient. Three patients (60%) had only

one sentinel node as metastatic disease in the neck. If more than one sentinel lymph node positive, it is likely that other lymph node(s) are involved.

Occult metastasis:

Occult metastases are those that are identified by enhanced techniques after being missed on a standard evaluation. They may be micrometastases that are identified only by serial sectioning, immunostaining, or RT-PCR. The table 28 shows the evidence from the available literature on occult metastasis.

Table 28: Occult Metastases

Study	**No. of Patients**	**Occult Metastases**
Beyers et al (1999)[93]	227 SOHND	42%
Mira et al (2002) [95]	126 SOHND	11%
De zinis et al (2006) [96]	89 (SOHND+RND)	52%
Iype et al(2008) [97]	184 SOHND	24.3 %
Legoux et al [98]	77 (62 SOHND+ 15 RND)	32.5%

Our data has shown 4/32 (12.5%) patients had occult disease which is in par with the recent literature. However none of our patients had extra capsular disease.

Neck dissection:

Pitman KT et al [99] comparing the modified radical neck and selective neck dissection for clinically N0 neck in 436 patients, showed regional recurrence rate of 5.8% for MRND and 3.5 % for selective neck dissection. The Brazilian Head and Neck Cancer Study Group [100] compared neck recurrence and survival for selective and modified radical neck dissection. In that study the regional control and overall 5-year survival rates were 87.5% and 67% in the selective neck dissection group and 89.3 % and 63% for MRND group respectively. This data suggest that the selective

neck dissection is oncologically comparable to conventional MRND for management of N0 neck

In our study sentinel node assisted neck dissection study out of the 32 patients 5 patients underwent MRND-1 and 27 patients had extended Supra Omo-Hyoid (SOHD) neck dissection.

Necessity of Level IIB, IV and V clearance:

The necessity of Level IIB clearance in oral cavity cancers with N0 disease is still debated due to the associated increased chance of injury to spinal accessory nerve and subsequent shoulder syndrome, since the risk of level IIB involvement is 2-6% [(102-105)]. In our study, none of sentinel nodes were identified in the level IIB. Moreover out of 98 nodes dissected in the level IIB in 32 patients with a mean of 3 nodes per neck dissection none revealed metastasis. Hence level IIB sparing neck dissection is sufficient if SLNB is negative.

Similarly, in clinically N0 neck involvement of level IV and V are rare [(107,108)]. In our study we have dissected 114 nodes with a mean of 3 nodes per patient in level IV. In level V a total of 22 nodes were harvested but all were histologically benign.

Recurrence:

A study by Carvalho AL[(101)] et al found that elective neck dissection is often used as a staging procedure, but recurrence has been found in 4.5% of the cases and this occurred either in the area of neck dissection (57.1%) or beyond (42.9%). Considering the six hypothetic scenarios: "only SLN removal", "SLN level dissection", "neck dissection from the tumour site to SN level", "selective neck dissection of three levels (SOHND)", "dissection from level I to IV"(extended

SOHND) and "comprehensive I-V dissection"(MRND), neck recurrences could be expected in 6.5%, 3.8%, 2.18%, 2.73%, 1.09% and 1.09% of cases, respectively

In our study 2 patient developed recurrences, both occurred in the contralateral neck. The first patient developed recurrence after 2 months and second patient after 4 months. One had T3 disease and the other had a 3.5 cm tumour. Both presented after 8 months of symptom and had carcinoma tongue. They had sentinel nodes in ipsilateral IB, IIA which was negative on frozen section and histo-pathological examination. Adequate nodes were sampled (16 & 31) in the two patients and all were negative. But on cytokeratin IHC one patient (T3) was positive for micro metastases. This is due to not sampling the contralateral side because of non-utilisation of radio colloid technique.

Disadvantages of our study:

1. Need to raise subplatysmal flap to identify sentinel lymph node.
2. Contralateral drainage cannot be identified.
3. Blue dye stains peritumoral areas making resection margin determination difficult
4. Difficulty in injecting 2 ml in case of hard palate and alveolar subsites(bony).
5. Blue dye tracking from the peritumoral areas to neck level from FOM lesion makes identification of SLN difficult.
6. Small sample size.

SUMMARY OF RESULTS:

In our study of 32 patients we had male: female 75%:25% ratio with mean age of 43.15 yrs (range: 26-70). Tongue (56.3%), buccal mucosa are the two common sub-sites, FOM is the least common. In western literature, buccal mucosa is the least common subsite as opposed to Indian population. This disparity is due to peculiar habit of using smokeless tobacco among our people. Our study included 19 smokers, 9 using tobacco quid and 10 were alcoholics. Carcinoma of oral tongue was the most common cancer among the smokers (p= 0.056). Our patients presented with ulcer (56.3%), or ulcer with pain (37.5%) and most have ulcero-proliferative (50%) type of tumor morphology. Right and left sided lesions are in equal distribution. 53.12% of patients reported for treatment after 3-4 month of symptoms and < 12.5% of patients presented within two months.

In this SLNB study, 50%, 43.7%, 6.3% are T1, T2, T3 tumors, 59.3%, 37.5% and 3.2% tumors were grade 1, 2 and 3 respectively and USG neck was not helpful in detecting occult metastatic nodes.

In this pilot study methylene blue dye based SLNB was done (not standard practice in head and neck cancer) and all patients electively followed with neck dissection. Sentinel lymphnode identification rate was 90.7% and 50 (mean 1.56) sentinel nodes were identified. Retro-molar trigone had the highest yield of SLN (mean 2.5) per patient; hard palate had least with (mean 1) node per patient. Level IIA was the most common level for SLN (17.2%) positivity for occult metastasis on frozen section. Out of the five patients all were carcinoma tongue and 60% of them were T1, grade -1 tumor and 40% were T2 tumor and 20% were grade 2, 3 tumor. In these patients 88% of SLN were positive for occult metastasis.

Enhanced pathological review facilitated to identify false positive and false negative on HPE, 3 patients were upstaged by IHC. Sensitivity, specificity and negative predictive value of sentinel node biopsy for using frozen section was 50%,95.2 %,83.3% and 80%, 95.8%, 95.8% when enhanced pathological review or IHC was used. In all patients on whom SLNB was non identifiable, histopathological examination of neck dissection specimen were also negative.

Non-smokers (15.6%) and non-alcoholic (9.3%) are at more risk for nodal metastasis than smokers & alcoholic (6.2%). T1 and T2 tumors have 12.5% and 21.4% pathological node positivity rates. Increasing grade conferred increased risk of nodal metastasis. In our study of sentinel node assisted neck dissection, 15.6% underwent MRND-1 and 84.4% SOHD.

In this study no sentinel nodes were identified in the level IIB, nor did any nodes positive in this level on neck dissection. Hence Level IIB sparing neck dissection may be recommended if SLNB is negative. In this pilot trial we did not encounter any skip metastasis, extracapsular disease, soft tissue deposit or overflow phenomenon. Peppering of nodes occurred in 40% patients and fast tract node occurred in 3.12%. Sentinel node as the only site of metastatic disease occurred in 60% and if more than one sentinel lymph node was involved other node(s) in the same or other level is likely to be involved as well.

Our data had shown occult disease in 12.5% of clinically N0 patients. However none our patients had extra capsular disease. 6.25% patient developed recurrences in the contralateral neck. This reveals the disadvantage of not sampling the contralateral side for these patients since only methylene blue dye was used.

CONCLUSION

Sentinel Lymphnode Biopsy (SLNB) addresses some of the complex issues of the management of clinically neck node negative oral cavity cancers. SLNB is still in early stages of development for head and neck cancers. This pilot study has shown that using blue dye alone to identify SLNB, does not meet recommended standard due to the lower sentinel lymphnode identification rate and mean node harvest.

This study has also shown other important results:

1. **The sensitivity, specificity and negative predictive value of sentinel node biopsy improved when enhanced pathological review or IHC incorporated in the protocol. Hence two staged sentinel procedure including both may be considered for further studies.**
2. Level IIA, IB is the most common site of sentinel nodes from oral cancers.
3. USG imaging is not useful in assessment of occult neck metastases as it is observer dependent.
4. SLNB using methylene blue alone has high Negative Predictive Value.
5. Absence of sentinel node metastasis has good correlation with negative non-sentinel nodes.
6. **No incidence of nodal metastases in Level IIB, IV and V in clinically N0 oral cancers. Routine dissections of these levels may be reconsidered among N0 patients to reduce morbidity.**

We anticipate a broader role for SLNB in future for staging and management of clinically node negative head and neck cancers. Radiocolloid localisation, IHC, Intraoperative RT-PCR and other molecular techniques may improve accurate identification of SLNB and detection of micro metastases.

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ABBREVIATIONS

DFS	Disease free Survival
FOM	Floor of Mouth
HPE	Histopathological Examination
ITC	Isolated Tumour Cells
LN	Lymph Node
LS	Lymphoscintography
Mi	Micrometastases
MRND	Modified Radical Neck Dissection
N+	Clinically Node Positive
N0	Clinically Node Negative
RLND	Regional Lymph Node Dissection
RMT	Retromolar Trigone
RND	Radical Neck Dissection
RT-PCR	Reverse Transcriptase – Polymerase chain Reactions
SAN	Spinal Accessary Nerve
SCC	Squamous Cell Carcinoma
SLN	Sentinel Lymph Node
SLNB	Sentinel Lymph Node Biopsy
SND	Selective Neck Dissection
SOHND	Supra omohyoid Neck Dissection

PROFOMA

Sr.No…… IP.NO……..

Name……. Age……. Sex a) Male b) Female

Date of admission: Date of surgery: Date of discharge:

Address……. Occupation…….

Patient History:

Religion: a) Hindu b) Christian c) Muslim d) others

Marital status: a) Married b) Unmarried c) Widow

Family H/o Cancer: a) Yes b) No c) Don't know

Family h/o Head and neck cancer: a) Yes b) No If YES: details:

Any pre- cancerous lesion or condition: ……..

Habits: a) Yes b) No If yes: a) tobacco chewing b) pan c) smoking d) alcohol

Duration: a) <1 yr b) 1-5 yr 3) > 5 yr.

Co-morbid factors a.DM b.HT c. IHD d. COPD e. Others: specify……

Previous Neck surgery: a)Yes b)No **If Yes – Excluded** Previous treatment of primary ……

Symptoms : Duration of symptoms in months a) 1 b) 2-3 c) 4-6 d) >6

local pain		ulcer		Bleeding		Aspiration	
Trismus		Dysphagia		Referred otalgia		Hypersalivation	
Voice Change		Neck swelling		Others			

Examination:

Number of lesions a) single b) Multiple.

Side a) Right b) Left c) Midline d) Bilateral e) Crossing midline

Type of growth a)Ulcero-proliferative b)verrucous c)infiltrative

Size of lesion a) Length ……cms b)Breadth…….cms

Extension to adjacent sites a)yes b)no If yes specify……

Clinical Neck Nodes a)Yes b)No **If Yes – Excluded**

USG Neck ……

Diagnosis: Clinical T N0 M0 a)Stage-1 b)Stage-2 c)Stage-3 d)Stage-4

Pre op HPE…… Grade ….....

Management:

Surgical treatment of neck: a) SOHND b) MRND c) RND

Surgical reconstruction: a) Nil b)PMMC c) DP d) Forehead e) others

Sentinel Node Biopsy details				
Level	**No. of Nodes**	**Frozen Section Positive/Negative**	**Final HPE Positive/Negative/ Micro metastases/ ITCs**	**Cytokeratin Positive/Negative**
IA				
IB				
IIA				
IIB				
III				
IV				
V				

Elective Neck Dissection details		
Level	**No. of Nodes**	**Final HPE:Positive/Negative/ Micro metastases/ ITCs**
IA		
IB		
IIA		
IIB		
III		
IV		
V		

Adjuvant Details: A) Chemotherapy B) Radiotherapy C) Others

Details of Chemo/RT……

Recurrence in primary			
Nodal recurrence			
Metastasis			
Others			

Details of Treatment of recurrence ……..

INFORMED CONSENT

SL NO …….. IP NO…….

Name…….. Age ……. Sex……

Date of Admission …… Date of surgery……..

Address……..

I'm suffering from oral cavity cancer. This cancer frequently affects lymphnodes and later it spreads to distant sites. Multimodality approach like Surgery, Radiotherapy and Chemotherapy are used to treat such cancer. Neck dissection surgery is treatment for cancer involvement of neck nodes in which lymphatic tissues are removed as a part of treatment. Neck dissection may lead to minor complication like seroma formation or at times major complications like bleeding and it can be acute , sub-acute or chronic. Few of which are bleeding at the time of surgery or delayed, air-way obstruction, nerve damage, chylous fistulae, infection, flap necrosis etc…

Alternative treatment includes Radiotherapy to neck and you have 100% right to refuse to participate in this project. Department of surgical oncology, GRH, Chennai-14 has started a project with the aim to diagnose involvement of neck nodes before they become palpable and will facilitate to identify early spread of cancer to neck and plan accurate treatment. We will first use the blue dye to identify sentinel node and then proceed to Selective Neck Dissection (SND) /Modified Radical Neck Dissection (MRND)/. Our research group will be very thankful for your support & co-operation.

I have studied and under-stood well all the points and I give free consent for my enrolment in above study whole heartedly.

Date:

Place: **Signature**

Signature of witness

Name & Contact no

Name	age	sex	IP no	Religion	Occupation	Family History	Comorbidities	Premalignant conditions	smoking	Alcohol	Tobacco chewing	Other Addictions	Symptoms	Symptom Duration	Site
mani	48	M	960025	hindu	watchman	normal	no	no	35 yrs	no	yes	hans	ulcer	24	buccal mucosa
thiruvenkadam	55	M	963039	hindu	flower vendor	normal	no	no	no	yes	30 yrs	no	ulcer	3	hardpalate
prema	40	F	962282	hindu	cooly	normal	no	no	no	no	no	no	ulcer, pain	2	tongue
viswanathan	55	M	963837	hindu	cooly	normal	ht	no	15 yrs	15 yrs	no	no	ulcer	8	tongue
baskar	43	M	964364	hindu	cooly	grand mother	ht	leucoplakia	no	no	20 yr	no	pain, ulcer	3	tongue
rathiannamal	58	F	964465	christian	home maker	normal	no	no	no	no	no	no	ulcer , otologia, hypersalivation	5	tongue
eallamal	70	F	964803	hindu	cooly	normal	no	no	no	no	40 yrs	no	ulcer	4	buccal mucosa
vijayakumar	32	M	964626	hindu	mechanic	normal	copd	no	7 yrs	no	5 yrs	pan	ulcer, pain	5	tongue
loganathan	56	M	967687	hindu	carpenter	normal	no	no	30 yrs	30 yrs	no	no	ulcer	6	tongue
varadarajan	60	M	966124	hindu	agriculturist	normal	dm	no	35 yrs	no	no	no	ulcer, pain	3	tongue
thangarasu	40	M	967446	hindu	electrician	normal	no	no	20 yrs	15 yrs	no	no	ulcer, pain	3	tongue
jeyaraj	54	M	968502	christian	agriculturist	normal	no	leukoplakia	30 yrs	no	no	no	ulcer	3	tongue
ramakrishnan	49	M	969310	hindu	cooly	normal	no	no	25 yrs	no	no	no	ulcer	3	buccal mucosa
lawrence	46	M	972058	christian	salesman	normal	no	no	no	no	no	no	ulcer	2	tongue
baradhan	70	M	972950	hindu	cooly	normal	no	no	40 yrs	35 yrs	no	no	ulcer	5	tongue
vasantha	55	M	975161	hindu	home maker	normal	no	no	no	no	no	no	ulcer	1	buccal mucosa
jeyaraman	62	M	976100	hindu	gardner	normal	no	no	30 yrs	no	10 yrs	pan	ulcer, pain dysphagia	6	tongue
kannumayil	62	F	976016	hindu	cooly	normal	no	no	no	no	no	no	ulcer, pain	8	tongue
marimuthu	51	M	982487	hindu	agriculturist	normal	no	no	25 yrs	no	no	no	ulcer	4	buccal mucosa
nagaraj	31	M	982423	hindu	cooly	normal	no	no	15 yrs	10 yrs	no	no	ulcer, pain	4	tongue
rebel	58	M	985045	christian	cooly	normal	no	no	25 yrs	no	no	no	ulcer, pain	3	tongue
sekar	55	M	983674	hindu	cooly	normal	no	no	23 yrs	20 yrs	no	no	ulcer	1	fom
velayutham	42	M	988608	hindu	cooly	normal	no	no	20 yrs	no	no	no	ulcer. Pain	3	rmt
varalakshmi	43	F	991452	hindu	home maker	normal	no	no	no	no	no	no	ulcer	3	tongue
veerasamy	65	M	991956	hindu	agriculturist	normal	no	no	36 yrs	no	no	no	ulcer	4	buccal mucosa
illamalli	55	F	993341	hindu	cooly	normal	no	no	no	no	35 yrs	no	ulcer	6	alveolus
janakiraman	26	M	999676	hindu	mechanic	normal	no	no	12 yrs	10 yrs	no	pan 10 yrs	ulcer pain	4	tongue
kaliyaperumal	65	M	998266	hindu	agriculturist	normal	no	no	30 yrs	25 yrs	no	no	ulcer pain	5	rmt
parthiban	45	M	100674	hindu	salesman	normal	no	no	20 yrs	20 yrs	no	pan 15 yrs	ulcer	3	tongue
rama	47	F	102479	hindu	cooly	normal	no	post cricoid web	no	no	20 yrs	no	ulcer	3	alveolus
neela	45	F	111091	hindu	home maker	normal	no	no	no	no	no	no	ulcer, pain	6	buccal mucosa
krishna moorthy	57	M	111543	hindu	agriculturist	normal	no	no	no	no	30 yrs	pan 20 yrs	ulcer	3	hardpalate

Name	Size (largest diameter)	type of tumour	Number	Side	cT	Histopathology	Grade	Resection	Reconstruction	Neck dissection	Sentinel Node number	no. of Sentinel Nodes dissected	No. of Sentinel Nodes Positive on Frozen	Nodes IA	Nodes Positive IA	Nodes IB	Nodes Positive IB	Nodes IIA	Nodes Positive IIA	Nodes IIB	Nodes Positive IIB	Nodes III	Nodes Positive III
mani	4x3	ulceroproliferative	one	right	2	scc	1	Wide Local Excision	nasolabial	sohd	Ib, II	2	negative	2	0	1	0	6	0	5	0	1	0
thiruvenkadam		ulcer	one	left	2	scc	1	palatoalveolar resection	obturator	sohd	Ib	1	negative	3	0	3	0	10	0	2	0	3	0
prema	3x2	ulceroproliferative	one	right	2	scc	2	hemiglossectomy	nil	mrnd-1	Ib, Iia, III	3	positive	3	0	3	2	3	2	2	0	4	2
viswanathan	1.5 x 1	infiltrative	one	left	1	scc	3	hemiglossectomy	nil	mrnd-1	Iia	1	positive	2	0	5	0	2	0	5	0	8	0
baskar	3.5x 2	ulceroproliferative	one	left	2	scc	1	hemiglossectomy	nil	sohd	III	1	negative	3	0	3	0	10	0	2	0	10	0
rathiannamal	3.5x 2.5	ulceroproliferative	one	left	2	scc	2	hemiglossectomy	nil	sohd	Ib	1	negative	4	0	3	0	7	0	2	0	9	0
eallamal	1.5x1	verrucous	one	left	1	scc	1	Wide Local Excision	ssg	sohd	IB	1	negative	2	0	1	0	3	0	4	0	8	0
vijayakumar	1.5x 1	ulcer	one	left	1	scc	1	Wide Local Excision	nil	mrnd-1	Iia III	2	III positive	3	0	4	0	7	0	2	0	10	0
loganathan	2x 3	ulceroproliferative	one	right	2	scc	1	hemiglossectomy	nil	sohd	Ib, Iia	2	negative	4	0	8	0	3	0	2	0	5	0
varadarajan	2x 1.5	ulcer	one	right	1	scc	2	hemiglossectomy	nil	sohd	no	no	no	2	0	6	0	7	0	3	0	5	0
thangarasu	5x4	infiltrative	one	right	2	scc	1	hemiglossectomy	nil	mrnd-1	Ib, II	2	positive	1	0	3	2	5	1	6	0	5	0
jeyaraj	3.2x 1.5	infiltrative	one	right	2	scc	1	hemiglossectomy	nil	sohd	IIa,III	2	negative	2	0	4	0	2	0	1	0	2	0
ramakrishnan	3x2	ulceroproliferative	one	left	2	scc	2	Wide Local Excision	ssg	sohd	Ia, Ib	2+1	negative	3	0	2	0	4	0	6	0	3	0
lawrence	1X1.5	verrucous	one	right	1	scc	1	Wide Local Excision	nil	sohd	Ib	2	negative	3	0	3	0	4	0	3	0	2	0
baradhan	3x 2	ulcer	one	left	2	scc	1	hemiglossectomy	nil	sohd	no	no	no	3	0	2	0	4	0	2	0	3	0
vasantha	2x2	ulceroproliferative	one	right	1	scc	1	Wide Local Excision	ssg	sohd	no	no	no	0	0	2	0	5	0	2	0	4	0
jeyaraman	5x2	infiltrative	one	left	2	scc	2	hemiglossectomy	nil	sohd	Ib	2	negative	1	0	2	0	2	0	6	0	1	0
kannumayil	5x 2.5	ulceroproliferative	one	right	3	scc	1	hemiglossectomy	nil	sohd	Ib, II	2	negative	6	0	4	0	5	0	4	0	4	0
marimuthu	2x1	ulceroproliferative	one	left	1	scc	2	Wide Local Excision	ssg	sohd	Iia	1	negative	4	0	3	0	3	0	2	0	3	0
nagaraj	2x1.5	infiltrative	one	left	1	scc	1	hemiglossectomy	nil	sohd	Iia	1	negative	4	0	5	0	7	0	5	0	3	0
rebel	2x2	ulcer	one	left	2	scc	2	Wide Local Excision	nil	sohd	Ib	2	negative	3	0	4	0	3	0	4	0	12	0
sekar	2.5 x 1.5	ulceroproliferative	one	right	2	scc	2	Wide Local Excision + MM	local	sohd	ib	2	negative	3	0	6	0	6	1	2	0	1	0
velayutham	2x1.5	ulcer	one	right	1	scc	2	Wide Local Excision + MM	local	sohd	Iia	2	negative	6	0	1	0	4	0	1	0	7	0
varalakshmi	2x3	ulceroproliferative	one	right	1	scc	1	Wide Local Excision	nil	mrnd-1	Iia	1	positive	3	0	4	0	3	1	3	0	1	0
veerasamy	3.5x2	ulceroproliferative	one	left	1	scc	1	Wide Local Excision+ periosteum	local	sohd	Ia	1	negative	0	0	4	0	5	0	2	0	6	0
illamalli	2x2	ulceroproliferative	one	left	1	scc	1	palatoalveolar resection	obturator	sohd	Ib, Iia	2	negative	5	0	2	0	3	0	2	0	7	0
janakiraman	5x4	infiltrative	one	right	3	scc	1	hemiglossectomy	nil	sohd	Ia, Iia, III	3	negative	4	0	1	0	3	0	3	0	2	0
kaliyaperumal	2x1	ulceroproliferative	one	left	1	scc	2	Wide Local Excision+ MM	local	sohd	Ia, Iia	2+1	negative	0	0	2	0	2	0	2	0	1	0
parthiban	3.5x3	ulceroproliferative	one	right	1	scc	1	hemiglossectomy	nil	sohd	Iia	1	negative	3	0	2	0	4	0	2	0	10	0
rama	3x3	ulcer	one	right	1	scc	1	palatoalveolar resection	obturator	sohd	Iia	2	negative	0	0	3	0	6	0	5	0	6	0
neela	3x2	ulceroproliferative	one	left	2	scc	2	Wide Local Excision + MM	local	sohd	Ib	1	negative	3	0	7	2	2	0	4	0	1	0
krishna moorthy	2x1.5	ulcer	one	right	1	scc	2	palatoalveolar resection	obturator	sohd	Iia	1	negative	4	0	1	0	5	0	2	0	2	0

Name	Nodes IV	Nodes Positive IV	Nodes V	Nodes Positive V	Total Nodes	Total Nodes Positive	pT	pN	Post op Morbidity	Adjuvant Treatment	Recurrence	time to recurrence	Followup	Details	cytokeratin
mani	5	0	0	0	20	0	1	0	nil	no	nil	no	26		Negative
thiruvenkadam	4	0	0	0	18	0	1	0	nil	no	nil	no	26		Negative
prema	3	0	3	0	21	4	2	2b	nil	RT	nil	no	25		Positive
viswanathan	3	0	4	0	29	1	1	1	nil	no	nil	no	24		Positive
baskar	2	0	0	0	28	0	2	0	nil	no	nil	no	24		Negative
rathiannamal	2	0	0	0	27	0	2	0	nil	no	nil	no	25		Negative
eallamal	10	0	0	0	28	0	1	0	nil	no	nil	no	24		Negative
vijayakumar	7	0	5	0	38	0	1	0	nil	no	nil	no	23	false positive slnb	Negative
loganathan	3	0	0	0	25	0	2	0	nil	no	nil	no	23		Negative
varadarajan	0	0	0	0	23	0	2	0	nil	no	nil	no	23		no
thangarasu	7	0	6	0	33	1	2	1	nil	yes	nil	no	22		Positive
jeyaraj	1	0	0	0	12	0	2	0	nil	no	nil	no	22		Positive ITC
ramakrishnan	2	0	0	0	20	0	2	0	nil	no	nil	no	21		Negative
lawrence	3	0	0	0	18	0	1	0	nil	no	nil	no	21		Negative
baradhan	2	0	0	0	16	0	2	0	nil	no	nil	no	20		no
vasantha	2	0	0	0	13	0	1	0	nil	no	nil	no	19		no
jeyaraman	4	0	0	0	16	0	2	0	nil	yes	yes	4	19	dead	Negative
kannumayil	8	0	0	0	31	0	3	0	nil	yes	yes	2	15	dead	Positive ITC
marimuthu	5	0	0	0	22	0	1	0	nil	no	nil	no	15		Negative
nagaraj	6	0	0	0	27	0	1	0	nil	no	nil	no	15		Negative
rebel	1	0	0	0	27	0	1	0	nil	no	nil	no	14		Negative
sekar	12	0	0	0	31	0	2	0	nil	no	nil	no	14	false negative	Negative
velayutham	1	0	0	0	20	0	1	0	nil	no	nil	no	11		Negative
varalakshmi	6	0	4	0	21	0	1	1	nil	no	nil	no	10		Positive
veerasamy	5	0	0	0	22	0	1	0	nil	no	nil	no	9		Positive ITC
illamalli	5	0	0	0	24	0	1	0	nil	no	nil	no	8		Positive ITC
janakiraman	3	0	0	0	16	0	3	0	nil	yes	nil	no	7		Negative
kaliyaperumal	0	0	0	0	7	0	2	0	nil	no	nil	no	7		Negative
parthiban	2	0	0	0	23	0	1	0	nil	no	nil	no	6		Negative
rama	0	0	0	0	20	0	1	0	nil	no	nil	no	5		Negative
neela	0	0	0	0	17	2	2	2a	nil	no	nil	no	3		Negative
krishna moorthy	0	0	0	0	14	0	1	0	nil	no	nil	no	3		Negative